AALBORG UNIVERSITY

A COST-UTILITY ANALYSIS OF NT-PROBNP AS AN INITIAL RULE-OUT BIOMARKER FOR CHRONIC HEART FAILURE IN PRIMARY CARE

IN A DANISH HEALTHCARE SETTING

Master's Thesis 2023

Medical Market Access, Medicine with Industrial Specialization

The Faculty of Medicine, Aalborg University

AALBORG UNIVERSITY

Title: A cost-utility analysis of NT-proBNP as an initial rule-out biomarker for chronic heart failure in primary care. In a Danish healthcare setting.

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Semester: 10th semester, Medical Market Access

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Master's Thesis period: February 1st – June 1st, 2023

ECTS: 30

Pages: 55

Characters: 98,830

Appendix: A-F

Acknowledgment

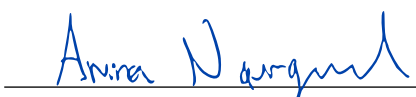
The authors would like to express their gratitude to Bianca Kennedy Hall, Stefan Christensen & their colleagues at AstraZeneca for their time and effort. Thank you to Matias Greve Lindholm & Karen Søeby from Zealand University Hospital, Roskilde for relevant information and support. Finally, but not least, a thank you to Flemming Witt Udsen for great support and supervision.

Forord

Specialet er udarbejdet på uddannelsen Medicin med Industriel Specialisering, Medical Market Access, på Aalborg Universitet i perioden februar til juni 2023 under supervision af Flemming Witt Udsen. Specialet er udarbejdet i eksternt samarbejde med AstraZeneca, der de seneste fire måneder har dannet rammerne for projektets tilblivelse med sparring og vejledning fra Sjællands Universitets Hospital, Roskilde. Specialet tager afsæt i en sundhedsøkonomisk analyse af konsekvenserne af rutinemæssig måling med biomarkøren NT-proBNP i almen praksis i Danmark, som et screeningværktøj til at opspore tidligere tegn på kronisk hjertesvigt forud for henvisning til ekkokardiografi. Ovenstående sammenlignes med nuværende praksis, hvor alle patienter med mistanke om kronisk hjertesvigt henvises direkte til en ekkokardiografi i sekundær sektor. Analysen inkluderer relevante effekter og omkostninger ud fra et sundhedssektorperspektiv, hvor resultatet i dette tilfælde er omkostninger per QALY efter implementering af NT-proBNP i almen praksis. Yderligere er der udarbejdet en budget-konsekvens analyse til at belyse budgetkonsekvenserne for regionerne ved implementering af biomarkøren NT-proBNP over fem år sammenlignet med standard praksis. Analysen er målrettet sundhedsprofessionelle, studerende på uddannelsen Medical Market Access og andre med interesse og viden indenfor sundhedsøkonomi. Litteraturliste inklusive litteraturhenvisninger er opbygget efter Harvard referencesystem.

Til sidst, en særlig tak til vores interne vejleder Flemming Witt Udsen samt eksterne samarbejdspartnere Bianca Kennedy Hall og Stefan Christensen fra AstraZeneca for en lærerig og meningsfuld afslutning på vores uddannelse.

Aalborg Universitet, 1 juni 2023



Anna Steen Nørgaard

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Abstract

Background: Chronic heart failure represents a major public health challenge. In Denmark, there is an increasing incidence, leading to a growing economic burden and societal strain. The current diagnostic strategy involves referring all patients for echocardiography based on a clinical examination. However, a promising and less costly rule-out biomarker, NT-proBNP, exists and has demonstrated effectiveness in primary care while resulting in cost savings. Several international guidelines recommend the use of NT-proBNP, however, there is inconsistency regarding an appropriate threshold for the general population. Despite these recommendations, NT-proBNP has not been fully implemented in Denmark. Therefore, this Master's thesis aims to investigate the cost-effectiveness of NT-proBNP compared to the standard of care and different thresholds in a Danish setting. Additionally, to clarify the budgetary consequences of the implementation of NT-proBNP.

Method: A cost-utility analysis was performed using a decision tree comparing three strategies; the standard of care, initial screening with NT-proBNP at a threshold of 125 pg/ml, and a threshold of 400 pg/ml from a healthcare perspective over a year. Moreover, deterministic and probabilistic sensitivity analyses were conducted to assess the uncertainties of the base case. Also, a budget-impact analysis over five years was performed including a scenario with a lower price for the NT-proBNP laboratory analysis.

Two systematic literature searches were conducted to identify existing evidence on the use of NT-proBNP in primary care and cost analyses, respectively.

Results: The strategy with an NT-proBNP threshold of 400 pg/ml was found to be cost-effective compared to the other strategies due to lower costs and greater health benefits, with a robust result to uncertainties. The implementation of NT-proBNP would result in savings of DKK 2-60 million over five years compared to the standard of care, potentially increasing to above DKK 80 million if the costs for NT-proBNP laboratory analysis decrease.

Conclusion: In conclusion, the implementation of NT-proBNP in primary care in Denmark is cost-effective. A threshold of 400 pg/ml was deemed cost-effective; however, it might be associated with a higher risk of missing diagnoses due to interpersonal differences, comorbidities, phenotypes, and risk factors.

Resume

Baggrund: Kronisk hjertesvigt udgør, med sin stigende forekomst, en betydelig udfordring for folkesundheden i Danmark, hvilket medfører en økonomisk byrde og et øget pres på samfundet. Den nuværende diagnostiske strategi for hjertesvigt indebærer henvisning af alle patienter til ekkokardiografi baseret på en klinisk vurdering. En lovende og besparende biomarkør, NT-proBNP, er tilgængelig og har vist sig at være effektiv i primærsektoren. Anvendelsen af NT-proBNP anbefales i flere internationale retningslinjer, men der er uenighed vedrørende en passende tærskelværdi for den generelle population, og NT-proBNP er fortsat ikke fuldt implementeret i Danmark. Derfor har denne kandidatafhandling til formål at undersøge omkostningseffektiviteten af NT-proBNP sammenlignet med den nuværende standardprocedure samt forskellige tærskelværdier i en dansk kontekst. Desuden at undersøge budgetkonsekvenserne af implementeringen af NT-proBNP.

Metode: En cost-utility-analyse blev udført ved brug af et beslutningstræ, som sammenlignede tre strategier, herunder den nuværende standardprocedure, brugen af NT-proBNP ved en tærskelværdi på henholdsvis 125 pg/ml og 400 pg/ml, ud fra et sundhedsperspektiv over et år. I forlængelse heraf blev der udført deterministiske og probabilistiske følsomhedsanalyser for at vurdere usikkerhederne i analysen. Ydermere blev der udført en budgetkonsekvensanalyse over en femårig periode, inklusive et scenario med en lavere pris for NT-proBNP laboratorieanalyse. Der blev udført to systematiske litteratursøgninger for at identificere eksisterende evidens vedrørende anvendelsen af NT-proBNP i primærsektoren samt omkostningsanalyser for NT-proBNP.

Resultater: Strategien med en NT-proBNP-tærskelværdi på 400 pg/ml var omkostningseffektiv sammenlignet med de andre strategier på grund af lavere omkostninger og større sundhedsfordele. Implementeringen af NT-proBNP ville medføre besparelser på 2-60 millioner kroner over en femårig periode sammenlignet med den nuværende standardprocedure og kunne stige til over 80 millioner kroner, hvis omkostningerne for NT-proBNP laboratorieanalyser faldt.

Konklusion: Det konkluderes, at implementering af NT-proBNP i primærsektoren i Danmark er omkostningseffektivt. En tærskelværdi på 400 pg/ml blev vurderet som omkostningseffektiv, men det tyder på, at den er forbundet med en større risiko for oversete diagnoser på grund af interpersonelle forskelle, komorbiditeter, fænotyper og risikofaktorer.

List of abbreviations

ACE: angiotensin-converting enzyme

BIA: budget-impact analysis

BMI: body mass index

BNP: B-type natriuretic peptide

CBA: cost-benefit analysis

CEA: cost-effectiveness analysis

CEAC: cost-effectiveness acceptability curve

CHEERS: Consolidated Health Economic Evaluations Reporting Standards

CI: confidence interval

CUA: cost-utility analysis

DAM: decision analytic model

DRG: diagnosis-related group

DSA: deterministic sensitivity analysis

ECG: electrocardiography

Echo: echocardiography

EF: ejection fraction

ESC: European Society of Cardiology

GP: general practitioner

HFmrEF: heart failure with mildly-reduced ejection fraction

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

HRQoL: health-related quality of life

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th revision

ICER: incremental cost-effectiveness ratio

ISPOR: the Professional Society for Health Economics and Outcomes Research

LVEF: left ventricular ejection fraction

N/A: not applicable

NICE: National Institute for Health and Care Excellence

NMB: net monetary benefit

NPV: negative predictive value

NT-proBNP: amino pro-B-type natriuretic peptide

NYHA: New York Heart Association

PICO: population, intervention, comparison, and outcome

POCT: point-of-care-testing

PPV: positive predictive value

PSA: probabilistic sensitivity analysis

QALY: quality-adjusted life-year

REFER: REFer for EchocaRdiogram

SE: standard error

SoC: standard of care

UHFO: Utrecht HartFalen Onderzoek

UK: United Kingdom

WTA: willingness-to-accept

WTP: willingness-to-pay

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1. Introduction

Chronic heart failure represents a major public health challenge in developed countries and is associated with poor quality of life and high healthcare resource consumption, with cardiovascular diseases as one of the leading causes of mortality in Denmark (European Commission 2017). Heart failure not only burdens individuals but also place a significant strain on healthcare systems globally, accounting for approximately 2% of total healthcare expenditures (Vestergaard et al. 2020). Hospital admissions are acknowledged as the primary contributor to the total costs related to heart failure, though outpatient visits also constitute a substantial part (ibid.). Approximately 66,000 patients in Denmark suffer from chronic heart failure with around 11,000 newly diagnosed patients annually (The Danish Heart Association 2018). Furthermore, according to Højbjerg (2016) about 10,000 additional people have decreased heart function without clinical significance. Despite the development and approval of several effective therapies within recent years, the prevalence is increasing, resulting in increased costs and decreased quality of life as more individuals risk being hospitalised or passing away (Jensen et al. 2023; Tanase et al. 2019). The increasing prevalence is partly attributed to a higher prevalence of predisposing factors such as hypertension, diabetes, obesity, and increased longevity (Vestergaard et al. 2020; Jørgensen et al. 2022). In Denmark, the average age of being diagnosed with chronic heart failure is 72 years, whereas the frequency increases with age (Kjærgaard 2021). Furthermore, approximately 5% of the Danish population over the age of 75 have heart failure, while the number increases to more than 10% at the age of 85 (ibid.).

Patients with heart failure may present with a variety of symptoms e.g., gradual onset of dyspnoea, fatigue, and ankle swelling (Højbjerg 2016). Unfortunately, these symptoms are non-specific, and often present in other medical conditions in general practice (Hildebrandt et al. 2010). Thus, some patients may not be appropriately investigated increasing the risk of corresponding under- and overtreatment (ibid.). To initiate appropriate treatment, early and accurate diagnosis is crucial. Echocardiography (echo) is the current standard of care for detecting left ventricular systolic dysfunction and other structural cardiac abnormalities (Mueller et al. 2019). However, its cost, limited availability, and complexity in assessing chronic heart failure make it an expensive and impractical choice for population screening (Mueller et al. 2019; Monahan et al. 2017). This leaves an unmet need for a more widely available initial rule-out biomarker for chronic heart failure in primary care.

Today, different biomarkers are used for screening various diseases including different types of cancers, neurological, kidney, and gastrointestinal diseases, among others (Califf 2019). Mueller et al. (2019) suggest natriuretic peptides as gold standard biomarkers for the diagnosis and prognosis of heart failure, as they are beneficial for screening to identify or exclude cardiac disease (ibid.). B-type natriuretic peptide (BNP) and its derivative, amino pro-B-type natriuretic peptide (NT-proBNP) are the two main natriuretic peptides that are biologically different (McDonagh et al. 2022; Berg et al. 2015). BNP is a biologically active hormone whereas NT-proBNP is inactive and is passively cleared from the body (ibid.). Thus, NT-proBNP has a longer half-time and as a consequence, circulates in higher concentrations within the blood, meaning it is more sensitive for detecting earlier forms of heart failure (ibid.). An ideal biomarker for initial heart failure assessment should be cost-effective, simple to use, have a prognostic impact and have a high negative predictive value (NPV) (Hildebrandt et al. 2010). In continuation, a health economic analysis conducted in the United Kingdom (UK) in 2017 revealed that using NT-proBNP as a rule-out biomarker of heart failure is cost-effective compared to other strategies including direct referral for an echo (Monahan et al. 2017; NICE 2018). Natriuretic peptides are increasingly used internationally, but despite being available for more than a decade, neither a rational implementation nor national or regional clinical guidelines exist in Denmark (Jørgensen et al. 2022). As a consequence, all patients are referred directly for an echo in case of suspected chronic heart failure, despite a rapid medical technology assessment was conducted in Denmark in 2018, suggesting that NT-proBNP screening prior to an echo was either cost-saving or cost-effective (Løvschall et al. 2018). Continuing to refer all patients directly for an echo will presumably increase waiting time leading to delayed diagnosis and initiation of treatment but also occupy specialized resources that could be used elsewhere. NT-proBNP could potentially improve the detection of chronic heart failure as well as reduce healthcare costs within the Danish healthcare system. The rule-out biomarker may also provide additional health for money compared to referring all patients for an echo, as the standard practice today. An essential, yet currently unavailable strategy to pre-select candidates eligible for an echo to confirm or exclude chronic heart failure exist, however, the rule-out biomarker has not been fully implemented in Denmark.

1.1. Main objective

The primary objective of this Master's thesis is to investigate the cost-effectiveness of NT-proBNP as an initial rule-out biomarker for chronic heart failure prior to an echo in primary care in Denmark from a healthcare perspective over one year. Furthermore, to assess an appropriate rule-out threshold for the trade-off between missed diagnoses and unnecessary echos. Lastly, this thesis aims to investigate the budgetary consequences over five years of implementing NT-proBNP compared to the standard of care.

2. Background

In the following section, the pathophysiology of chronic heart failure, including its screening and diagnostic algorithm will be reviewed. In addition, the section will focus on the biochemistry of natriuretic peptides and their role in screening and diagnostics of chronic heart failure, including threshold values for NT-proBNP and the lack of agreement among different guidelines.

2.1. Heart failure pathophysiology

Heart failure is a syndrome, a combination of signs and symptoms, caused by an impairment of the heart's pumping mechanism and as a result, the heart cannot maintain sufficient cardiac output to meet the body's metabolic demands (Schwinger 2021). Heart failure is typically characterised by cardinal symptoms (e.g., dyspnoea, fatigue, ankle swelling), that may be accompanied by clinical signs (e.g., peripheral oedema, jugular vein stasis, crepitation on lung auscultation) caused by structural and/or functional cardiac abnormalities resulting in decreased cardiac output and/or elevated intracardiac pressures during rest or light exertion (ibid.). This often leads to myocardial damage or a prolonged strain on the myocardium, leading to changes in the left ventricle in the form of dilation and hypertrophy (Schwinger 2021). These changes lead to peripheral vasoconstriction, fluid retention and thus decreased blood flow to the organs (ibid.). Common causes of heart failure include coronary artery disease, high blood pressure, valvular heart disease, and atrial fibrillation, among others (Schwinger 2021). Heart failure may occur acutely (e.g., myocardial infarction) or chronically (e.g., hypertension) and is classified according to the affected circulatory system, right-sided and/or left-sided heart failure (Løgstrup et al. 2023). Left-sided heart failure occurs when the left ventricle is gradually weakened, whereas right-sided heart failure usually occurs as a result of left-sided heart failure, where the left ventricle fails and fluid pressure is transferred back through the lungs, eventually damaging the right ventricle (ibid.). Heart failure can additionally be classified into different phenotypes based on the ejection fraction (EF), expressed as the percentage, of how much blood the left ventricle pumps out with each contraction (Rogers 2022). The different phenotypes include heart failure with reduced EF (HFrEF), preserved EF (HFpEF), and mildly-reduced EF (HFmrEF) depending on the left ventricular ejection fraction (LVEF), which currently are defined as ≤40%, ≥50%, and in-between, respectively (Løgstrup et al. 2023; Tanase et al. 2019). HFrEF is the most common phenotype in primary care in Denmark accounting for 43.19% of all cases, followed by recovered HFrEF (30.71%), while the remaining cases are caused by HFpEF and HFmrHF (Jensen

et al. 2023). Furthermore, physicians usually classify a patient's heart failure according to the New York Heart Association (NYHA) Functional Classification based on the extent of heart failure (McDonagh et al. 2022). A patient is placed in one of four categories based on the severity of the symptoms in regard to normal breathing and varying degrees of angina and/or shortness of breath, and how much the patient is limited during physical activity (ibid.).

2.2. Screening and diagnosing chronic heart failure in primary care

The diagnosis of chronic heart failure is based on detailed patient history, objective findings, clinical manifestations and paraclinical examinations (Løgstrup et al. 2023). Yet, since many of the symptoms are non-specific and difficult to distinguish from those of other diseases, diagnosing chronic heart failure can be challenging, especially in the early stages (Løgstrup et al. 2023; Baslund 2020). Danish current standard practice is to refer all patients for an echo based on a blood test, symptoms, and electrocardiography (ECG) (Kjærgaard 2021). Echo is the most crucial non-invasive test for all types of chronic heart failure, yet costly as it provides a detailed assessment of the severity of hemodynamic impact, chamber dimension, heart valve function, intracardiac pressure conditions, and wall thicknesses, among others (Baslund 2020; Monahan et al. 2017). As the Danish healthcare system operates on a limited budget, efficient use of resources is essential, and a rule-out biomarker for chronic heart failure in primary care should be considered. In addition, a Swedish retrospective study has, however, slightly indicated a financial benefit of using the biomarker NT-proBNP as a rule-out biomarker for heart failure in general practice before referral for an echo (Khezri et al. 2014). In continuation, the Danish Society for General Medicine recommends that local guidelines for the use of NT-proBNP to be prepared, based on existing national and regional guidelines (Heebøll-Nielsen & Holme 2013). The overall purpose of NT-proBNP is to improve the selection of patients so that unnecessary referrals for an echo are avoided and further investigation to identify the triggering factor can proceed. Currently, the Danish Society of Cardiology suggest delaying an echo until other, more probable disorders have been ruled out if a patient with a low-to-intermediate risk of heart failure has normal ECG and NT-proBNP levels are within the normal range (Løgstrup et al. 2023). However, no specific cut-off values for NT-proBNP were mentioned in their updated national guidelines for chronic heart failure (ibid.).

2.2.1. Natriuretic peptides as biomarkers in chronic heart failure

Natriuretic peptides are biomarkers measurable in the bloodstream which can be used to diagnose and monitor chronic heart failure (Januzzi 2013). As mentioned, the two main natriuretic peptides used in clinical practice include BNP and NT-proBNP (Berg et al. 2015: McDonagh et al. 2022). The BNP gene is activated in cardiomyocytes in response to increased cardiac hemodynamic stress due to volume- and/or pressure-overload states (Kim & Januzzi 2015). BNP secretion, therefore, causes a reduction in filling pressure and vascular resistance by increasing water and salt excretion within the kidneys, which causes vasodilation and has inhibitory effects on the sympathetic nervous system and renin-angiotensin-aldosterone system (Kim & Januzzi 2015; Kerkelä 2015). The BNP gene activation results in the production of an intracellular precursor propeptide (proBNP), where additional processing of the propeptide results in the release of the biologically inert amino-terminal fragment (NT-proBNP) (Berg et al. 2015). BNP and NT-proBNP are released in a 1:1 ratio, however, the measured NT-proBNP level is higher than BNP as NT-proBNP is more passively cleared from the circulation (ibid.). BNP elimination is dependent on receptor-mediated cellular uptake and enzymatic degradation, whereas the elimination of NT-proBNP may be obligately dependent on renal glomerular filtration rate, why normal plasma levels of BNP and NT-proBNP differ significantly (Berg et al. 2015; Jernberg et al. 2006). Circulating levels of BNP and NT-proBNP usually are very low in healthy individuals and an appropriate rule-out value must have a high sensitivity and NPV without compromising specificity too much in order to exclude a substantial number of patients while missing as few as possible (Hildebrandt et al. 2010). As mentioned, NT-proBNP is a more stable peptide with a longer half-time compared with BNP, why routine use of NT-proBNP could be an appropriate rule-out biomarker prior to an echo for patients with suspected heart failure in primary care (Hildebrandt et al. 2010; Berg et al. 2015). Prospectively, NT-proBNP will be the primary focus of this Master's thesis.

2.2.1.1. NT-proBNP threshold values and influencing factors

Various guidelines and recommendations are available for the use of NT-proBNP as an initial rule-out biomarker for chronic heart failure in primary care settings (McDonagh et al. 2022; NICE 2018; Mueller et al. 2019). However, in general, there seems to be a lack of consensus regarding appropriate NT-proBNP threshold values. For instance, the National Institute for Health and Care Excellence (NICE) guideline for chronic heart failure recommends that a patient with an NT-proBNP level ≥400 pg/ml should be referred for an echo, whereas the European Society of Cardiology (ESC) guideline

recommends referral for an echo if the NT-proBNP level is ≥125 pg/ml (NICE 2018; McDonagh et al. 2022). The lack of consensus may be brought on by the fact that more cardiac patients live with risk factors and comorbidities, which can have a distinct influence on NT-proBNP blood levels by down- or up-regulating (Simmonds et al. 2020). The different phenotypes may also have an impact as the HFpEF phenotype often is preceded by non-cardiac comorbidities such as inflammation, obstructive pulmonary disease, and age with consequential low-grade cardiac inflammation, whereas the HFrEF phenotype is often preceded by acute or chronic loss of cardiomyocytes due to ischaemia, valvular disease, myocarditis, or a genetic mutation (see *Figure 2.1.;* ibid.). Obesity, hypertension, diabetes, and renal insufficiency are comorbidities that can lead to both HFrEF and HFpEF and thereby influence the NT-proBNP blood level (ibid.). Several studies have indicated that HFrEF mainly occurs in male patients and is a consequence of myocardial infarction, whereas HFpEF or HFmrEF mainly occurs in females with a higher body mass index (BMI) and higher systolic blood pressure, indicating that sex also may play a crucial role (Jensen et al. 2023; Simmonds et al. 2020). In continuation, Remmelzwaal et al. (2020) reported that the detection of HFpEF in an outpatient population is difficult as the levels of NT-proBNP are usually low as opposed to patients with HFrEF.

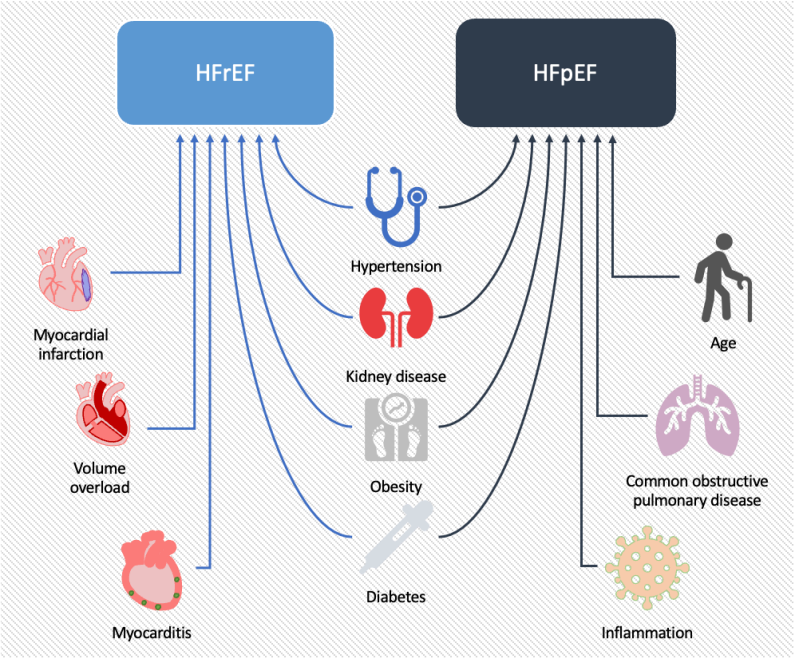

Figure 2.1. The figure illustrates the risk factors and comorbidities involved in the development of either HFrEF and/or HFpEF. Inspired by: Simmonds et al. 2020.

The heart failure phenotype along with comorbidities and risk factors in the underlying patient populations may be the explanation for the differences observed in the threshold values for the ESC

and NICE guidelines. An individual patient data meta-analysis estimated the performance characteristics of the NT-proBNP thresholds in primary care settings recommended by ESC and NICE guidelines and found that the ESC guideline thresholds of ≥125 pg/ml were more accurate at detecting HFrEF phenotype than HFpEF in a primary care setting (Roalfe et al. 2022). Another explanation may be the trade-off between the diagnostic precision and the willingness to miss a diagnosis in exchange for lower costs; whereas in ESC, the first is prioritised, NICE tends to prioritise cost-effectiveness. In a recently published position paper from the Danish Society of Cardiology (2021), age-dependent thresholds for NT-proBNP in primary care settings are presented, corresponding to ≥125 pg/ml for patients aged between 50-74 and ≥300 for patients ≥75 years. The position paper presents an algorithm (see *Figure 2.2.*) for investigating patients with suspected heart failure in general practice (ibid.). The above-mentioned may suggest different reasons why defining a universal cut-off threshold prior to referral for an echo remains a challenge. Due to the lack of established guidelines in Denmark, this Master's thesis will investigate whether the established thresholds for ESC and NICE are cost-effective compared to the Danish standard practice in primary care.

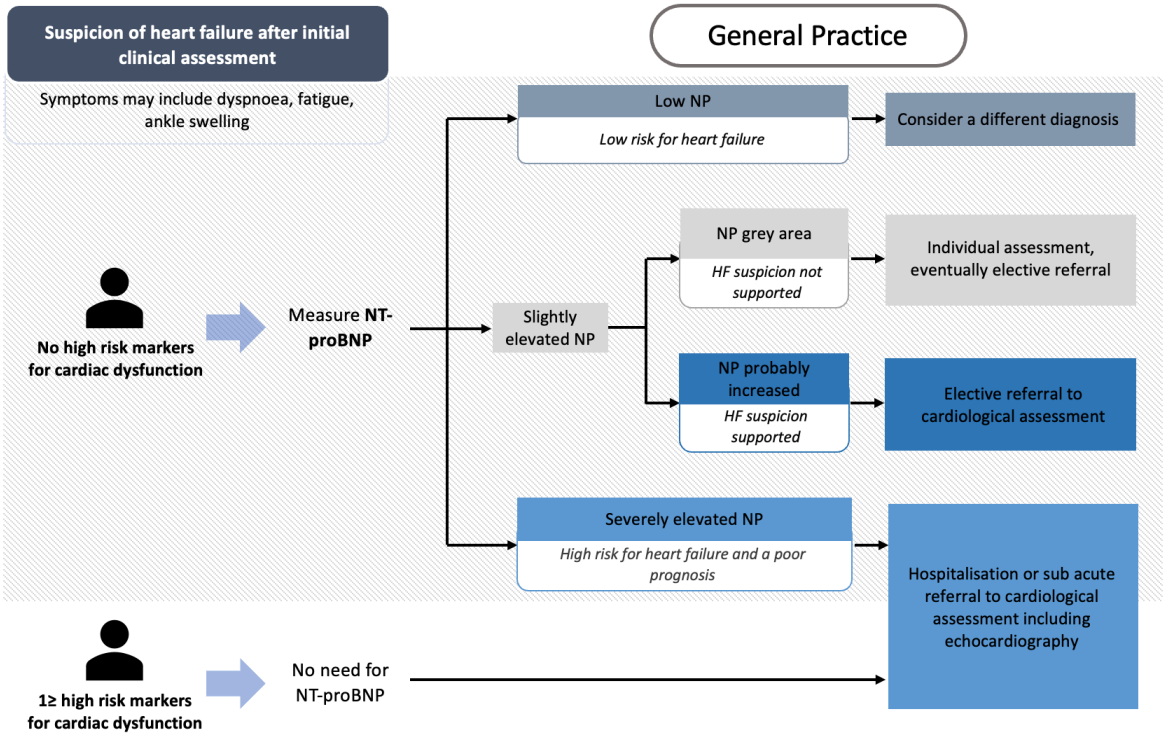

Figure 2.2. The figure illustrates a patient flow in general practice following initial NT-proBNP screening with age-dependent thresholds. High-risk markers for cardiac dysfunction include previous acute myocardial infarction, several years with dysregulated hypertension/diabetes, clinical symptoms such as dyspnoea and fatigue, and electrocardiography abnormalities, among others. Inspired by: The Danish Society of Cardiology 2021.

3. Method

The following section will describe the methodological approaches applied for the economic evaluation, followed by a presentation of the decision analytic model (DAM). Furthermore, the procedures for conducting systematic literature searches to identify model inputs will be elaborated on followed by the applied method underlying different sensitivity analyses. Finally, the method behind the budget-impact analysis (BIA) will be presented. The economic evaluation was reported in accordance with the Consolidated Health Economic Evaluations Reporting Standards (CHEERS) checklist (Husereau et al. 2022). Furthermore, the BIA was conducted in accordance with the Professional Society for Health Economics and Outcomes Research (ISPOR) Principles for Good Practice for BIA II over a five-year time horizon (Sullivan et al. 2014).

3.1. Economic evaluation

The purpose of an economic evaluation is to inform decision-makers about which alternative healthcare intervention should be recommended, approved for widespread use, and reimbursed for specific patient groups (Drummond et al. 2015). An economic evaluation is a comparative analysis of the costs and consequences of two or more alternative healthcare interventions (ibid.). There are several cost analyses, however, only three full economic evaluations exist considering both costs and consequences, namely, a cost-effectiveness analysis (CEA), a cost-utility analysis (CUA), and a cost-benefit analysis (CBA) (Drummond et al. 2015). The identification and valuation of costs in monetary values are identical across the analyses, but the nature of the consequences varies considerably (ibid.). For instance, in the CEA the consequences are expressed as natural units (e.g., blood pressure reduction), and the result may be stated as incremental cost per unit of effect (ibid.). The CEA is typically provided in studies of preventative or diagnostic interventions because these tend to focus on the specific impact of the intervention rather than the patient's overall health (Drummond et al. 2015). Furthermore, a CEA may be applied in cases where a decision-maker with a limited budget must assess a limited range of possibilities within a certain field (ibid.). However, a disadvantage of the CEA is that it is challenging to assess opportunity costs across disease areas covered by the same budget (ibid.). A CUA is a variant of a CEA with the effect measure being utility. Health-related Quality of Life (HRQoL) is frequently used to quantify utility, which when combined with life-years, yields quality-adjusted life-years (QALY) (Drummond et al. 2015). The greatest advantage of a CUA is that it provides the potential to compare healthcare interventions across different healthcare areas

given the generic effect measure, allowing for the assessment of opportunity costs when adopting a new intervention to achieve the highest amount of welfare possible (ibid.). While a CEA considers how to best allocate an existing budget, a CBA considers whether expanding the budget is worthwhile (Drummond et al. 2015). The aforementioned requires expressing the consequences in monetary terms by converting health measures into monetary values that can be interpreted alongside costs (ibid.). This Master's thesis will apply a CUA with QALY as the effect measure.

The question when deciding between alternatives is whether the additional or incremental health benefits of one intervention over another are sufficient to justify the additional or incremental costs (Drummond et al. 2015). In some cases, the choice between alternatives is obvious; for example, if one alternative provides greater health benefits at lower costs or if it is less effective but has higher costs, then the alternative is said to be dominant or dominated, respectively, in the comparison of two alternatives (ibid.). However, if an alternative provides both additional health benefits and higher costs, or the opposite, fewer health benefits and lower costs, the decision is based on how much the decision-maker is willing to pay to gain one additional unit of effect or how much the decision-maker is willing to save to accept the loss of a unit of effect, defined as willingness-to-pay (WTP) and willingness-to-accept (WTA), respectively (ibid.). WTP and WTA thresholds depend on opportunity costs, meaning what is likely to be sacrificed as a consequence of the additional costs or the values of what is foregone compared with the health benefits (Drummond et al. 2015). If a cost-effectiveness decision depends on WTP or WTA, an incremental cost-effectiveness ratio (ICER) can be used to express the relationship between the incremental cost and health benefit of two alternatives as a support in relation to allocating resources: (Drummond et al. 2015)

$$ICER = \frac{\Delta C}{\Delta E} = \frac{Cost_{intervention} - Cost_{comparator}}{Effect_{intervention} - Effect_{comparactor}}$$

When two alternatives are examined, a simple ICER can be used to summarise the cost-effectiveness of selecting a more effective but more expensive alternative or less effective and less expensive as just one comparison of incremental cost and effect is possible (ibid.). However, there are frequently additional alternatives accessible, and an economic evaluation should consider all relevant alternatives (ibid.). As a result, a wide range of ICERs can be reported as several alternatives necessitate multiple pairwise comparisons with varying incremental costs and health benefits (Drummond et al. 2015). Which comparisons should be made are determined by the reported expected values for costs and health benefits. For example, if one alternative has higher costs but

lower health benefits than another alternative, it is said to be strongly dominated and should never be chosen regardless of a WTP threshold (ibid.). It is, therefore, crucial to exclude strongly dominated alternatives as other alternatives will appear beneficial when compared to exceptionally poor alternatives and thereby recommend on an incorrect foundation (ibid.). Following the removal of strongly dominated alternatives, one may investigate extendedly dominated alternatives by comparing alternatives with pairwise ICERs and progressing from the least costly to the next more costly and effective alternative (Drummond et al. 2015). If the ICER associated with moving to a more effective alternative decreases, then the lower-cost alternative used to calculate the ICER is extendedly dominated (ibid.). Both strongly and extendedly dominated alternatives may be removed, resulting in the appearance of a recommendation for a cost-effective alternative (ibid.).

3.1.1. Net monetary benefit

An ICER compared to a threshold, k, ($ICER < k$) is equivalent to determining whether the incremental net health benefits provided by the intervention are positive, or whether the incremental net monetary benefit (NMB) is positive, as expressed by: (Drummond et al. 2015)

$$\Delta NMB = k * \Delta E - \Delta C$$

When there are multiple alternatives, cost-effectiveness expressed in terms of NMB is especially useful as it does not require only pairwise comparisons (Drummond et al. 2015). In contrast to ICER, only the NMB of each alternative must be determined, not the incremental net benefit of each pair of alternatives, because comparing the NMBs of any two alternatives is equivalent to calculating the incremental NMB of this comparison (ibid.). The alternative that provides the greatest NMB at a given WTP threshold is deemed cost-effective (ibid.). NMB requires a pre-specified WTP threshold, which at present does not exist in Denmark (Drummond et al. 2015). However, a threshold of DKK 200,000 was applied based on the widely accepted UK NICE threshold values of £20,000-30,000, which corresponds to DKK168,648-252,972 (exchange rate GBP100=DKK843.24, April 17th, 2023) (Danmarks Nationalbank 2023; McCabe et al. 2008).

3.2. Decision analytic model

A DAM provides a framework for decision-making under uncertain conditions in a systematic way as it enables the combination of evidence from various sources which, when combined with explicit assumptions and judgements, provide estimates of costs and health benefits (Drummond et al. 2015).

In general, a set of mathematical relationships between entities, which typically are health states or pathways characterising a variety of disease prognoses and the effects of the alternative interventions, is defined by a DAM (ibid.). By accumulating the entities, the costs and health benefits of interest for an economic evaluation are predicted (ibid.).

The two most common DAMs include a decision tree and a Markov model. A decision tree is the preferred method for acute diseases as it can handle a few health states in a short time horizon and only allows forward movement in the model, meaning that progression through the model is dependent on previous events (Drummond et al. 2015). Time is, however, not explicitly defined in a decision tree as events are implicitly assumed to occur over an instantaneous discrete period, making time-dependent elements difficult to implement (ibid.). A Markov model, on the other hand, is the preferred method for chronic or relapse-remitting diseases as it can handle multiple health states and a long-time horizon with incorporated time cycles; however, it is memoryless (the Markovian assumption), and the transition probability is independent of previous transitions (ibid.). Even though heart failure is a chronic condition that gradually tends to get worse over time, a decision tree was applied as the presented problem in question contains a few stages that occur only once, extend over a short period of time and transitions from one event to another are dependent on each other. In addition, the screening process with NT-proBNP is of short duration and one generally receives a diagnosis within one year defining the time horizon of the model. To identify all relevant resources for the investigation, an appropriate perspective is necessary. There are three distinct perspectives, the narrow hospital, the healthcare, and the broad societal perspective (ibid.). The hospital perspective considers costs related to the hospital (e.g., admission and ambulatory care), while the healthcare perspective further includes costs related to the primary care sector (e.g., general practice). Additionally, the societal perspective covers costs related to the secondary and primary care sector, municipalities, and productivity loss (Ehlers & Vestergaard 2019). A healthcare perspective was deemed appropriate in order to cover the disease-related costs. Furthermore, assumptions are necessary and unavoidable in a decision tree as it simplifies the real world, see *Appendix A* for the model assumptions.

3.3. Structure of the Decision Tree

The decision tree was constructed in TreeAge Pro 2023 (Healthcare Version). Theoretically, a decision tree begins with a decision node, represented by a square, which indicates the choice between the alternatives and can only occur once. The branches from the decision node represent the

alternatives. A branch may be followed by a circle, which represents a chance node, indicating that a patient has varying probabilities of experiencing one of the following events. The specific probabilities are associated with the branches that follow a chance node. Finally, a triangle represents a terminal node indicating an endpoint beyond which a patient cannot progress. A simple decision tree is illustrated in *Figure 3.1.*

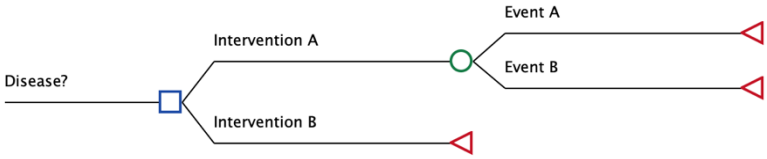

Figure 3.1. The figure illustrates a simple decision tree comparing two interventions and associated events.

The average patient presenting with suspected heart failure is 72 years. The model does not take phenotypes, comorbidities, or risk factors into consideration. Moreover, it is assumed that all patients will have their NT-proBNP blood serum tested in the NT-proBNP strategies, even though high-risk patients will be directly referred for an echo in most guidelines. In the model, there are three screening strategies after initial examination for patients who turn to their general practitioner (GP) due to suspected heart failure; 1) the patient is referred directly for an echo, 2) the patient is initially screened using NT-proBNP with a referral threshold for an echo of 125 pg/ml, or 3) the patient is initially screened using NT-proBNP with a referral threshold for an echo of 400 pg/ml. As illustrated in *Figure 3.2.*, the model begins with a decision node, indicating a decision between the three above-mentioned screening strategies. The clinical course of each strategy will be explained in more detail in the following, whereas the use of resources will be explained later.

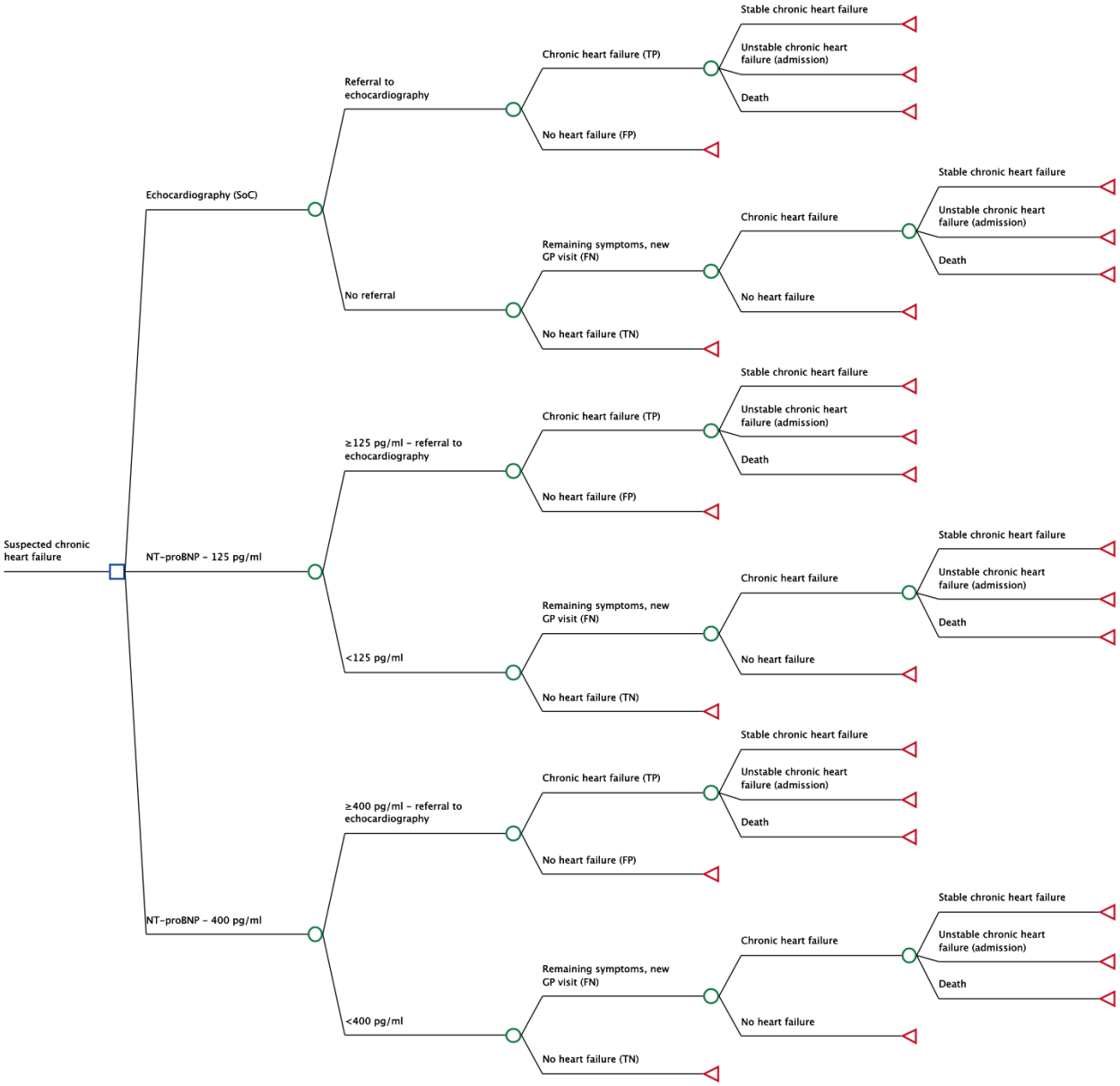

Figure 3.2. The figure illustrates the decision tree for the three screening strategies for patients with suspected chronic heart failure: 1) the patient is referred directly for an echocardiography (echo), 2) the patient is initially screened using NT-proBNP with a referral threshold for an echo of 125 pg/ml, or 3) the patient is initially screened using NT-proBNP with a referral threshold for an echo of 400 pg/ml.

3.3.1. Echocardiography (Standard of Care)

According to the standard of care of general practice a patient with symptoms suggestive of heart failure can after a clinical examination either be referred for an echo or not. A patient that is directly referred for an echo will subsequently receive a final diagnosis of heart failure or not. The majority of patients diagnosed with heart failure are assumed to have stable disease and initiate outpatient management, however, there is a risk of passing away. Of the patients receiving outpatient

management, some will be admitted due to an unstable disease. If no heart failure diagnosis is received, the patient does not advance further.

An undiagnosed patient with heart failure not referred for an echo is assumed to return to general practice due to persistent symptoms of heart failure within six months. Following it is assumed that the patient is directly referred for an echo, resulting in a true positive diagnosis of heart failure, and will subsequently follow the same clinical course as a patient diagnosed with heart failure, except for an increased risk of unstable disease or passing away. The standard of care strategy is visualised in *Figure 3.3*.

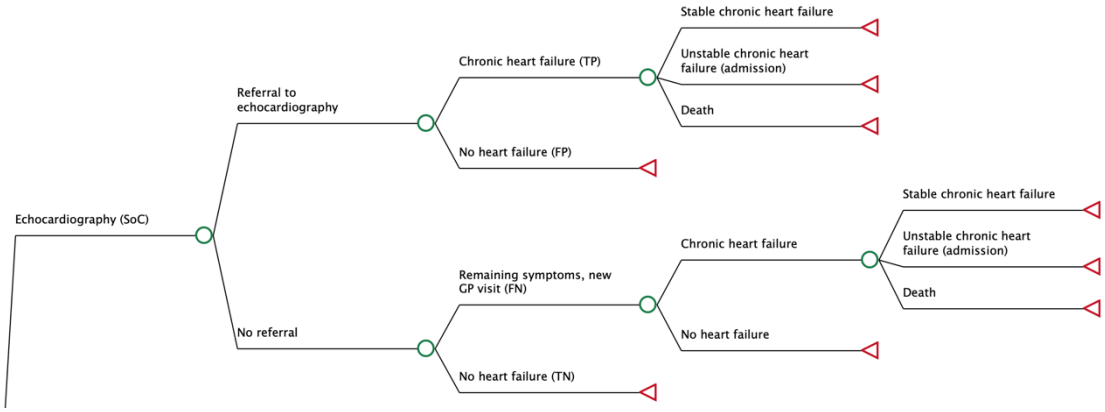

Figure 3.3. The figure illustrates the standard of care strategy, where a patient may be referred for an echocardiography (echo) based on the clinical examination. If a patient is referred for an echo the chronic heart failure diagnosis may be confirmed or dismissed; if the latter is the case, the patient will not proceed in the model. In case of a confirmed diagnosis, a patient will either have stable disease and receive outpatient management, experience deterioration in disease that necessitates admission or risk passing away. If, on the other hand, a patient is not referred for an echo, there is a chance of a true negative diagnosis or a missed diagnosis, which presumably will necessitate a second visit to general practice and subsequently a referral for an echo.

3.3.2. Screening with biomarker NT-proBNP with a referral threshold of 125 pg/ml

For the screening strategy with the biomarker NT-proBNP with a referral threshold of 125 pg/ml, a patient with symptoms suggestive of heart failure will have their NT-proBNP blood serum tested prior to an echo referral. If the NT-proBNP blood serum level is greater than 125 pg/ml, the patient will be referred for an echo, where the diagnosis of chronic heart failure will either be confirmed or rejected. In case of a rejected diagnosis, the patient will not proceed in the model. If the chronic heart failure diagnosis is confirmed, the patient will follow the clinical course described in *Section 3.3.1*.

If the NT-proBNP blood serum level is less than 125 pg/ml the suspension of heart failure will be dismissed, which can result in two different outcomes; the decision to dismiss was correct, and the patient does not have chronic heart failure and will not proceed in the model, or the chronic heart

failure diagnosis has been missed by the GP. If the latter is the case, it is assumed that the patient will return to their GP within a year and be referred for an echo, resulting in a correct diagnosis of chronic heart failure. Following a correct diagnosis, the patient will follow the clinical course described in *Section 3.3.1.* The NT-proBNP 125 pg/ml strategy is visualised in *Figure 3.4*.

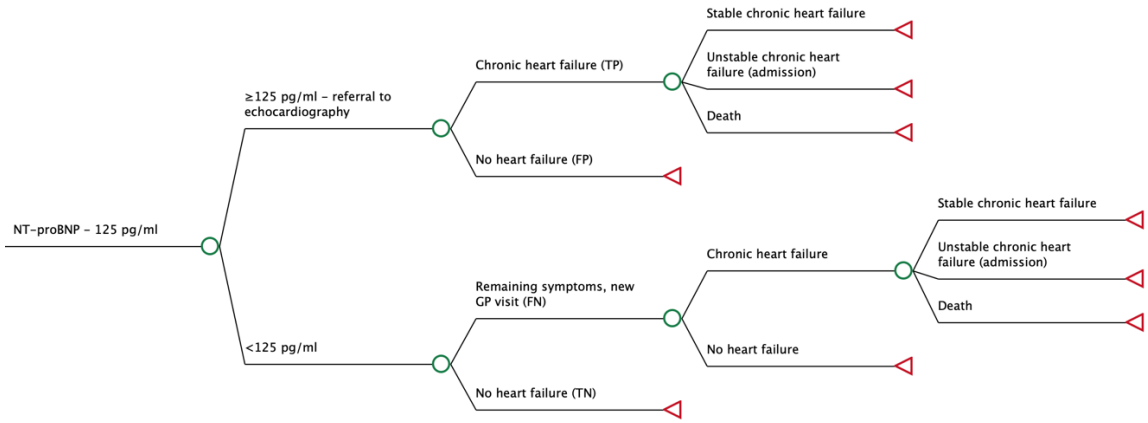

Figure 3.4. The figure illustrates the NT-proBNP with a threshold of 125 pg/ml strategy, where a patient based on a clinical examination and NT-proBNP level will be referred for an echocardiography (echo) or not. If a patient is referred for an echo the chronic heart failure diagnosis may be confirmed or dismissed; if the latter is the case, the patient will not proceed in the model. In case of a confirmed diagnosis, a patient will either have stable disease and receive outpatient management, experience deterioration in disease that necessitates admission or risk passing away. If, on the other hand, a patient is not referred for an echo, there is a chance of a true negative diagnosis or a missed diagnosis, which presumably will necessitate a second visit to general practice and subsequently a referral for an echo.

3.3.3. Screening with biomarker NT-proBNP with a referral threshold of 400 pg/ml

The screening strategy with the biomarker NT-proBNP with a referral threshold of 400 pg/ml is similar to the strategy described in *Section 3.3.2.*, with the exception that the current strategy applies an NT-proBNP threshold value of 400 pg/ml instead of 125 pg/ml. The NT-proBNP 400 pg/ml strategy is visualised in *Figure 3.5*.

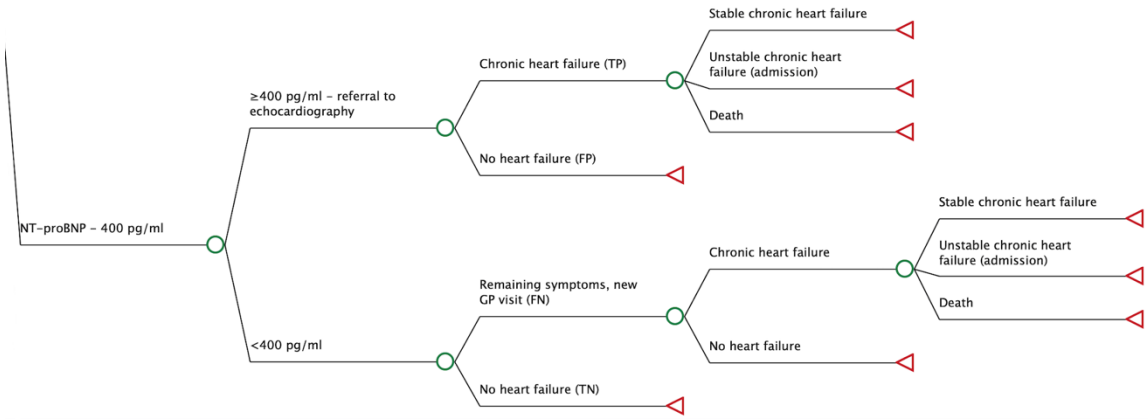

Figure 3.5. The figure illustrates the NT-proBNP with a threshold of 400 pg/ml strategy, where a patient based on a clinical examination and NT-proBNP level will be referred for an echocardiography (echo) or not. If a patient is referred for an echo the chronic heart failure diagnosis may be confirmed or dismissed; if the latter is the case, the patient will not proceed in the model. In case of a confirmed diagnosis, a patient will either have stable disease and receive outpatient management, experience deterioration in disease that necessitates admission or risk passing away. If, on the other hand, a patient is not referred for an echo, there is a chance of a true negative diagnosis or a missed diagnosis, which presumably will necessitate a second visit to general practice and subsequently a referral for an echo.

3.4. Systematic literature search

Two systematic literature searches were conducted to identify inputs for the model and to clarify the existing knowledge within the disease area. A systematic literature search allows the collection of all evidence available within a specific area of interest in a pre-planned, structured, and reproducible way (Aarhus University 2022). The method necessitates thoughtful consideration of both database selection and the use of search terms (ibid.).

The two searches were conducted on February 23rd and March 9th, 2023, respectively, in the scientific databases MEDLINE (PubMed) and Embase. MEDLINE (PubMed) is the preferred database among science researchers due to its extensive coverage with more than 29 million references to journal articles (Frandsen et al. 2021; National Library of Medicine 2022). However, MEDLINE (PubMed) has limitations as it does not cover health science research literature equally across specialities, and a search in MEDLINE (PubMed) alone is unlikely to yield all relevant evidence (Frandsen et al. 2021). As a result, searches in additional databases are required, therefore a literature search in Embase was conducted as well (ibid.). Embase contains over 10 million records not found in MEDLINE, as well as 2,900 unique journals (Elsevier 2023).

The *Population, Intervention, Comparison* and *Outcome* (PICO) model was used to define the two searches by using relevant search terms (Bramer et al. 2018). For both searches, the population included patients with suspected or confirmed heart failure and the intervention was the rule-out biomarker NT-proBNP. The first search focused on the application of NT-proBNP in primary care to identify relevant thresholds, as well as investigate the precision, sensitivity, and specificity of NT-proBNP at different cut-off values. The second search was focused on cost analyses in order to identify existing literature on the field along with collecting inputs for the model. An overview of the full searches can be found in *Appendix B* and *C*. As the searches were systematic, all references were screened for duplicates followed by an assessment of the title and abstract based on prespecified

inclusion and exclusion criteria. Finally, the full text of the chosen articles was read (see *Figure 3.6.; Table 3.1.*).

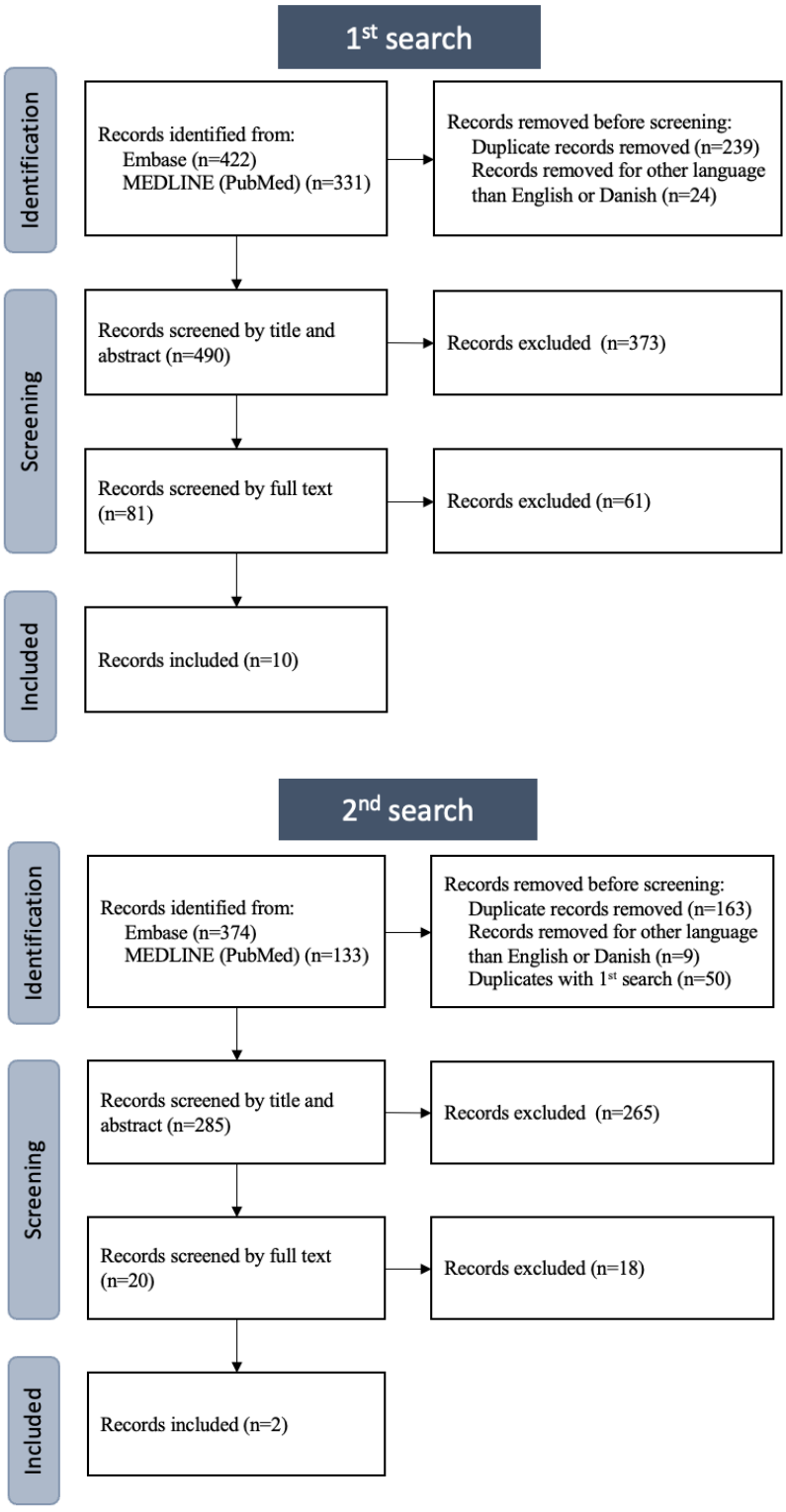

Figure 3.6. The figure depicts two flowcharts of the selection process for the systematic literature searches. Inspired by: Page et al. 2021.

Table 3.1. The table includes the inclusion and exclusion criteria for the systematic literature search.

Inclusion criteria	Exclusion criteria
Patients with suspected or confirmed chronic heart failure	Written languages other than Danish or English
Sensitivity and specificity	Non-western studies
Cost-analysis	Full-text not available
	Studies published before 2003

3.5. Model input

Model inputs including costs, utility weights and probabilities will be presented in the following section.

3.5.1. Estimating costs and resources

To identify and estimate all costs associated with the three strategies, a four-step approach was used: identification, measurement, and valuation of resource consumption, and lastly, total costs calculation (Drummond et al. 2015).

As mentioned, the healthcare perspective covering costs related to the primary and secondary sectors was utilised in the model. Diagnosis-related group (DRG) tariffs for 2023 were applied to estimate hospital costs associated with an echo and an admission. Costs related to primary care including blood sample collection, consultation and annual follow-up at general practice were extracted from a collective agreement for general practice using 2023 tariffs (Laeger.dk 2023). The cost for the NT-proBNP blood serum analysis was extracted from the public prices from the Department of Clinical Biochemistry, Bispebjerg Hospital (Capital Region 2023). Finally, the costs for medicines were extracted as the pharmacy purchase price from the official website for medicine prices in Denmark, Medicinpriser.dk (2023a, b, c). All costs were included as gamma distribution as they range from $0 \leq x < \infty$ (Drummond et al. 2015). See *Table 3.2.* for all costs included.

Table 3.2. The table includes input parameters for cost related to primary, secondary care and outpatient management.

Event	Mean (95% CI)	SE	Distribution	Notes	References
Annual control	416.47 (253.03;479.3)	83.29	Gamma	Code 0120 annually control at general practice	Laeger.dk 2023
Blood sample and analysis of NT-proBNP	255 (155.04;354.96)	51	Gamma		Capital Region 2023
Blood sample from vein per shipment	53.01 (32.23;73.39)	10,60	Gamma	Code 2101 blood sample applied as a cost per consultation	Laeger.dk 2023
Echocardiography	1,975 (1200.8;2749.2)	395	Gamma	Cost per echo. (DI500 (kronisk hjerteinsufficiens) + UXUC80 (Transtorakal ekkokardiografi)) DRG gruppe: 05PR04 Kardiologisk undersøgelse, udvidet.	Sundhedsdata Styrelsen 2023
Hospital admission	35,525 (21,599.2; 49,450.8)	7,105	Gamma	Cost for hospital admission	Sundhedsdata Styrelsen 2023
GP consultation	155.24 (94.39; 216.09)	31.05	Gamma	Code 0101 consultation applied as a cost per consultation	Laeger.dk 2023
Initiating medication	414.75 (252.17; 577.34)	82.95	Gamma	ACE inhibitor: Enalapril 2.5 mg x2 Beta-blockers: Metoprolol 25 mg x1 - SGLT-2 inhibitor: 5 mg x 2	Medicinpriser.dk 2023a, b, c
Medication, final	685.01 (416.49; 953.53)	137.00	Gamma	ACE inhibitor: Enalapril 10-20 mg x 2 Beta-blockers: Metoprolol 200 mg SQLT-2 inhibitor: 7.5 mg x 2	Medicinpriser.dk 2023 a, b, c

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; echo, echocardiography; GP, general practitioner; NT-proBNP, amino pro-B-type natriuretic peptide; SE, standard error.

*When possible, estimates of SE and 95% CI were obtained directly from the literature or data. Otherwise, the estimates were estimated based on either SE or relevant 95% CI. When the SE and 95% CI were not available, an assumed SE of 20% of the mean was used to calculate the 95% CI (CI=(mean-1.96*SE; mean+1.96*SE)).*

3.5.1.1. Cost inputs in the model

A visit to a GP includes the cost of a consultation and a blood sample where the cost is accounted for at each visit. For the NT-proBNP strategies, the cost of the NT-proBNP laboratory analysis is included for the initial visit at a GP. Also, the cost of an echo is calculated each time it is performed. Furthermore, outpatient management includes an annual control and two GP consultations. Lastly, hospital admission included the cost of the hospital stay as well as the cost for an annual control and two GP visits. All combinations of costs are shown in *Table 3.3*.

Table 3.3. The table gives an overview of the costs accounted for at different clinical activities.

Procedure	Costs
GP visit	GP consultation + blood sample
First GP visit in NT-proBNP strategies	GP consultation + blood sample + NT-proBNP analysis
Outpatient management	Annual control + 2 x GP consultations
Admission	Hospital admission + annual control + 2 x GP consultations

Abbreviations: GP, general practitioner; NT-proBNP, amino pro-B-type natriuretic peptide.

3.5.1.1.1. Medication

Medication consumption is based on guidelines from the Danish Society of Cardiology, suggesting start-up treatment with angiotensin-converting enzyme (ACE) inhibitors, beta blockers and SGLT-2 inhibitors where the dose may be up-regulated continuously depending on the patient need (Løgstrup et al. 2023). It is assumed that all patients referred for an echo following a clinical examination or an NT-proBNP serum level above the thresholds will initiate start-up treatment, the assumption was supported by a clinical expert in cardiology.

For the standard of care strategy, delayed access for an echo was expected due to increased waiting time. Therefore, it was assumed that the annual medication consumption included a start-up dose for two months, and in case of a confirmed diagnosis, medication was upregulated to full dose for 10 months (see *Table 3.4.*). For the NT-proBNP strategies, a confirmed diagnosis is assumed within a month, due to a shorter waiting time for an echo. Medication consumption was therefore assumed to include a start-up dose for one month and subsequently the full dose for 11 months in case of confirmed diagnosis (see *Table 3.4.*).

For all strategies, it was assumed that the average patient with persistent symptoms will return to their GP after six months and be referred for an echo, this assumption is in concordance with Monahan et al. (2017). The medication consumption is therefore assumed to include one month on the start-up dose and in case of a confirmed diagnosis, five months on the full dose.
An overview of included drug and associated calculations of the total monthly costs can be found in *Appendix D*.

Table 3.4. The table gives an overview of the duration of the medicine at initial and final dose counted for in the different strategies.

	Duration of initial dose (months)	Duration of final dose (months)
Direct referral for an echo (SoC)	2	10
Referral for an echo based on NT-proBNP level above threshold	1	11
Missed diagnosis (in all strategies)	1	5

Abbreviations: echo, echocardiography; NT-proBNP, amino pro-B-type natriuretic peptide; SoC, standard of care.

3.5.2. Quality-adjusted life-years

Utility and disutility weights were ascribed to health states to enable estimation of QALY for the three strategies. Utilities were extracted from the literature, with one estimate from Denmark, UK, and combined data from Austria and Canada, respectively (Hvidberg et al. 2023; Sullivan 2011; Moertl et al. 2013). The patient population was ascribed a baseline utility reflecting a starting age of 70-79 years extracted from Sullivan (2011) considering that in Denmark the average age at which a person is diagnosed with heart failure is 72 years (Kjærgaard 2021). A utility weight was applied for chronic heart failure extracted from a Danish catalogue of EQ-5D-3L QALY scores for chronic conditions (Hvidberg et al. 2023). Furthermore, a disutility was ascribed to patients admitted, and death was ascribed a utility weight of zero (Moertl et al. 2013). Utility values were beta-distributed as they range from $0 \leq x \leq 1$ whereas disutilities with a negative value were normal-distributed as they range from $-\infty < x < \infty$ (Drummond et al. 2015). Weights for estimation of QALY are presented in *Table 3.5*.

Table 3.5. The table include input parameters for utility/disutility weights.

Event	Utility weights (95% CI)	SE	Distribution	Notes	References
Baseline age-related utility	0.723 (0.713; 0.733)	0.0049	Beta	A utility value of age between 70 and 79 years	Sullivan et al. 2011
Utility related to chronic heart failure	0.678 (0.648; 0.708)	0.0151	Beta	Utility of ICD-10 I11.0: Hypertensive heart disease. I13.0: High blood pressure with both heart disease and kidney disease. I13.2: Hypertensive heart and chronic kidney disease with heart failure and with chronic kidney disease, or end-stage renal failure. I42.0: Cardiomyopathy I42.6: Alcoholic cardiomyopathy. I42.7: Cardiomyopathy caused by drug or other agent. I42.9: Cardiomyopathy UNS. I50.0: Heart failure. I50.1: Chronic heart failure. I50.9: Heart failure UNS	Hvidberg et al. 2023
Admission	-0.02 (-0.03; -0.01)	0.0051	Normal	A disutility associated with hospital admission	Moertl et al. 2013

Abbreviations: CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision, SE, standard error.

*When possible, estimates of SE and 95% CI were obtained directly from the literature or data. Otherwise, the estimates were estimated based on either SE or relevant 95% CI. When the SE and 95% CI were not available, an assumed SE of 20% of the mean was used to calculate the 95% CI (CI=(mean-1.96*SE; mean+1.96*SE)). SE is calculated based on the 95% CI using the following equation: SE = (upper limit-lower limit)/3.92.*

3.5.3. Probabilities

Probabilities were primarily extracted from European literature and the Danish Heart Failure Database. For transition probabilities where no data were available, an estimate confirmed by a clinical expert from Zealand University Hospital was utilised (see *Table* 3.6.)

Input parameters limited with the range of $0 \leq x \leq 1$, as for probabilities, were beta-distributed derivatives (Drummond et al. 2015).

Table 3.6. The table presents input parameters for the probabilities.

Event	Probability (95% CI)	SE	Distribution	Notes	References
Echocardiography (SoC)					
Proportion of patients referred for an echo	0.850 (0.517; 0.999)	0.170	Beta		Fonseca et al. 2022 + expert opinion
Proportion of patients referred for an echo who has HF	0.650 (0.395; 0.905)	0.130	Beta		Taylor et al. 2017
Proportion of patients referred for an echo after GP revisit	0.200 (0.122; 0.278)	0.040	Beta	Patient who revisits their GP due to persistent symptoms and are thereby referred for an echo	Fonseca et al. 2022 + expert opinion
Proportion of patients referred for an echo a second time who have HF	0.950 (0.578; 0.999)	0.190	Beta	Patient who visits their GP within one-year due to a putative HF diagnosis	Fonseca et al. 2022 + expert opinion
NT-proBNP threshold of 125 pg/ml					
Proportion of patients with NT-proBNP value above 125 pg/ml	0.658 (0.400; 0.916)	0.086	Beta		Taylor et al. 2017
Positive predictive value for 125 pg/ml	0.562 (0.305; 0.789)	0.123	Beta	PPV is used to determine the number of patients referred for an echo that actually have heart failure	Roalfe et al. 2021
Negative predictive value for 125 pg/ml	0.851 (0.805; 0.889)	0.021	Beta	NPV is used to determine the number of patients not referred for an echo that actually not have heart failure	Roalfe et al. 2021
NT-proBNP threshold of 400 pg/ml					
Proportion of patients with NT-proBNP value below 400 pg/ml	0.319 (0.194; 0.444)	0.064	Beta		Taylor et al. 2017
Positive predictive value for 400 pg/ml	0.683 (0.463; 0.844)	0.097	Beta	PPV is used to determine the number of patients referred for an echo that actually have heart failure	Roalfe et al. 2021
Negative predictive value for 400 pg/ml	0.799 (0.756; 0.837)	0.021	Beta	NPV is used to determine the number of patients not referred for an echo that actually not have heart failure	Roalfe et al. 2021
Common probabilities					
Probability of being admitted within 30 days	0.060 (0.036; 0.084)	0.012	Beta		RKKP 2023

after first contact with outpatient management				
1-year mortality probability	0.060 (0.036; 0.084)	0.012	Beta	RKKP 2023

Abbreviations: CI, confidence interval; echo, echocardiography; HF, heart failure; GP, general practitioner; N/A, not applicable; NT-proBNP, amino pro-B-type natriuretic peptide; SE, standard error.

*When possible, estimates of SE and 95% CI were obtained directly from the literature or data. Otherwise, the estimates were estimated based on either SE or relevant 95% CI. When the SE and 95% CI were not available, an assumed SE of 20% of the mean was used to calculate the 95% CI (CI=(mean-1.96*SE; mean+1.96*SE)).*

3.5.3.1. Probabilities in the model

Positive and negative predictive values from a meta-analysis were used to determine the number of patients with an NT-proBNP above and below the thresholds who have heart failure and who do not, respectively (Roalfe et al. 2021).

In the standard of care strategy, it was assumed that there was a slightly increased risk of an event due to waiting time for an echo, why a relative risk of 1.1 was multiplied by the risk of hospital admissions as well as the mortality risk. Also, patients with a missed diagnosis may have an increased risk of an event and a relative risk of 1.15 was applied. These assumptions are based on Fonseca et al. (2022) and supported by a clinical expert.

3.6. Sensitivity analysis

An economic evaluation is based on several assumptions and estimates, it is therefore, essential to assess to what extent uncertainties affect the result of the analysis using different sensitivity analyses (Drummond et al. 2015). The degree of uncertainty of the base-case result was investigated using both deterministic sensitivity analysis (DSA) as well as a probabilistic sensitivity analysis (PSA). Three types of uncertainty are related to an economic evaluation including parameter, methodological, and structural uncertainty (ibid.). Parameter uncertainty refers to a lack of perfect information and the fact that we do not know the true value of a given parameter (Bojke et al. 2009). Furthermore, methodological uncertainty includes differences in the analytic methods used to support an economic evaluation, such as the perspective or type of economic evaluation (ibid.). Finally, structural uncertainty refers to the simplifications and scientific judgements made when developing and interpreting a model, such as whether the model adequately captures all relevant characteristics of interventions and the disease (Bojke et al. 2009). A PSA can be used to investigate parameter

uncertainty, whereas DSA allows for investigating all types of uncertainty (Drummond et al. 2015). Both sensitivity analyses were conducted to systematically assess uncertainties and to investigate the robustness of the results.

3.6.1. Deterministic sensitivity analysis

A DSA can be used to demonstrate how sensitive the outcome of a model-based analysis is to changes in a single parameter or a group of parameters (Drummond et al. 2015). The analysis reflects the quantitative relationship between changes in input values and the corresponding model output values (ibid.). A DSA can be performed as a best-case-worst-case analysis in which model parameters are evaluated at extreme but plausible values with upper and lower boundaries (ibid.). This was done for all model parameters including costs, utilities, and probabilities, which were ascribed a range based on the 95% CI. When a 95% CI was not available, a symmetric range was applied based on the mean value of the parameter +/-1.96*SE. In cases, where the SE was unknown, 20% of the mean value was applied to reflect the associated uncertainty (see *Table 3.2., 3.5., 3.6.*).
The outcomes will be shown as NMB at a WTP threshold of DKK 200,000 per QALY and will be displayed in a Tornado diagram, where a parameter was designated as sensitive if its extreme values changed which intervention was assumed cost-effective. As a result, the analysis can indicate which parameters may affect the result at extreme, but plausible values.

3.6.2. Probabilistic sensitivity analysis

Unlike a DSA, a PSA can reveal how uncertain a decision might be as it can be used to explore the impact of the uncertainty surrounding the input parameters on the model result simultaneously (Drummond et al. 2015). This stochastic sensitivity analysis will be carried out using a 2nd order Monte Carlo simulation that randomly samples the parameter distributions 10,000 times (ibid.). The 10,000 iterations were visualised in a cost-effectiveness scatter plot that depicts the uncertainty around the cost and effect of the three strategies (Drummond et al. 2015). Furthermore, the cost-effectiveness acceptability curve (CEAC) was created to illustrate the likelihood of the three interventions being cost-effective at different WTPs (ibid.). Thereby, the CEAC can assist in quantifying the risk associated with a certain decision (ibid.).

3.7. Budget-impact analysis

A BIA may be included in a comprehensive economic assessment to support the CUA (Sullivan et al. 2014). A BIA considers the anticipated changes in the expenditure of a healthcare system after the adoption of a new intervention (ibid.). Furthermore, a BIA estimates the likely financial consequences of adopting a new intervention compared to the current intervention (ibid.). A BIA was performed to estimate the potential increase in cost or cost savings of using NT-proBNP as a rule-out biomarker for suspected chronic heart failure in the primary sector. The BIA was developed to test the hypothesis that using NT-proBNP would yield more accurate clinical decisions, reducing unnecessary referrals for an echo on patients without chronic heart failure, and hereby reducing false positives. Furthermore, giving an earlier and more accurate diagnosis of patients with the disease, reducing false negatives, allowing patients with chronic heart failure to start treatment earlier and ultimately obtain a better outcome (Monahan et al. 2017).

The target population included patients presenting at general practice with a suspicion of heart failure in Denmark, and the incidence of new patients in a five-year horizon was utilised. According to a clinical expert, approximately 23,000 patients with suspected heart failure are expected to visit their GP, with an annual increase of 1% due to better treatment of related diseases and people living longer (see *Table 3.7.*).

Table 3.7. The table present the number of new patients presenting at general practice with a suspicion of heart failure supported by a clinical expert (The Danish Heart Association 2018).

	Year 1	Year 2	Year 3	Year 4	Year 5
Incidence (Denmark)	23,000	23,230	23,462	23,697	23,964

The BIA included costs related to GP visits including blood sampling, NT-proBNP laboratory analysis and an echo (see *Table 3.8.*). Furthermore, the probabilities included in the BIA are shown in *Table 3.9.*

Table 3.8. The table includes the costs accounted for in the budget-impact analysis.

Procedure	Price (DKK)	Reference
NT-proBNP analysis	255	Capital Region 2023
GP consultation including blood sample	208.25	Laeger.dk 2023
Echocardiography	1,975	Sundhedsdata Styrelsen 2023

Abbreviations: GP, general practitioner; NT-proBNP, amino pro-B-type natriuretic peptide.

Table 3.9. The table presents the probabilities used in the budget-impact analysis.

Procedure	Probability	Reference
NT-proBNP ≥125 pg/ml	0.658	Taylor et al. 2017
NT-proBNP ≥400 pg/ml	0.319	Taylor et al. 2017
2nd GP visit in SoC	0.2	Fonseca et al. 2022 + expert opinion
2nd GP visit referral for an echo in SoC	1	Assumption
2nd GP visit in the 125 pg/ml strategy	0.149	Roalfe et al. 2021
2nd GP visit referral for an echo in the 125 pg/ml strategy	1	Assumption
2nd GP visit in the 400 pg/ml strategy	0.201	Roalfe et al. 2021
2nd GP visit referral for an echo in the 400 pg/ml strategy	1	Assumption

Abbreviations: echo, echocardiography; GP, general practitioner; NT-proBNP, amino pro-B-type natriuretic peptide; SoC, standard of care.

A scenario analysis including a lower price of the NT-proBNP analysis was conducted as it is expected that the price will decrease if the test becomes a permanent part of clinical practice. The price was changed to DKK 53 as suggested by a medical director from the Department of Clinical Biochemistry at Roskilde University Hospital.

4. Results

In the following section, results from the base-case analysis, the deterministic and probabilistic sensitivity analyses, and the results of the budget-impact analysis will be presented.

4.1. Base-case result

The base-case result indicated that implementing NT-proBNP as a rule-out biomarker prior to an echo with a threshold of 400 pg/ml is strongly dominant compared to the standard of care due to lower cost and higher utility, and to NT-proBNP with a threshold of 125 pg/ml due to the lower cost and slightly higher utility from a healthcare perspective. The expected accumulated costs were DKK 4,482, DKK 6,025, and DKK 7,913 and the expected accumulated QALY were 0.692, 0.686, and 0.670 for NT-proBNP 400 pg/ml threshold, NT-proBNP 125 pg/ml threshold, and standard of care, respectively (see *Table 4.1.*). The base-case results indicate that the implementation of the NT-proBNP 400 pg/ml strategy is deemed cost-effective irrespective of a willingness-to-pay threshold.

Table 4.1. The table presents the expected values of cost and utilities for the three strategies.

	NT-proBNP 400 pg/ml	NT-proBNP 125 pg/ml	Standard of care
Costs (DKK)	4,482	6,025	7,913
Utility (QALY)	0.692	0.686	0.670

Abbreviations: NT-proBNP, amino pro-B-type natriuretic peptide; QALY, quality-adjusted life-years; SoC, standard of care.

4.2. Deterministic sensitivity analysis

A one-way DSA was performed on the base-case analysis to determine whether, and which input parameters, have an impact on the outcome. The analysis compared all strategies, and the outcomes are represented as the NMB at a WTP threshold of DKK 200,000 per QALY. At this WTP threshold, the NMB of the three strategies was DKK 133,909, DKK 131,248, and DKK 126,093 for NT-proBNP thresholds of 400 pg/ml, 125 pg/ml, and the standard of care, respectively.

The Tornado diagram depicts the DSA results with a 20% variation, indicating that the greatest uncertainty was associated with the utility value for chronic heart failure (see *Figure 4.1.*). However, none of the bars reaches the NMB value for the two inferior strategies, indicating the robustness of the base case.

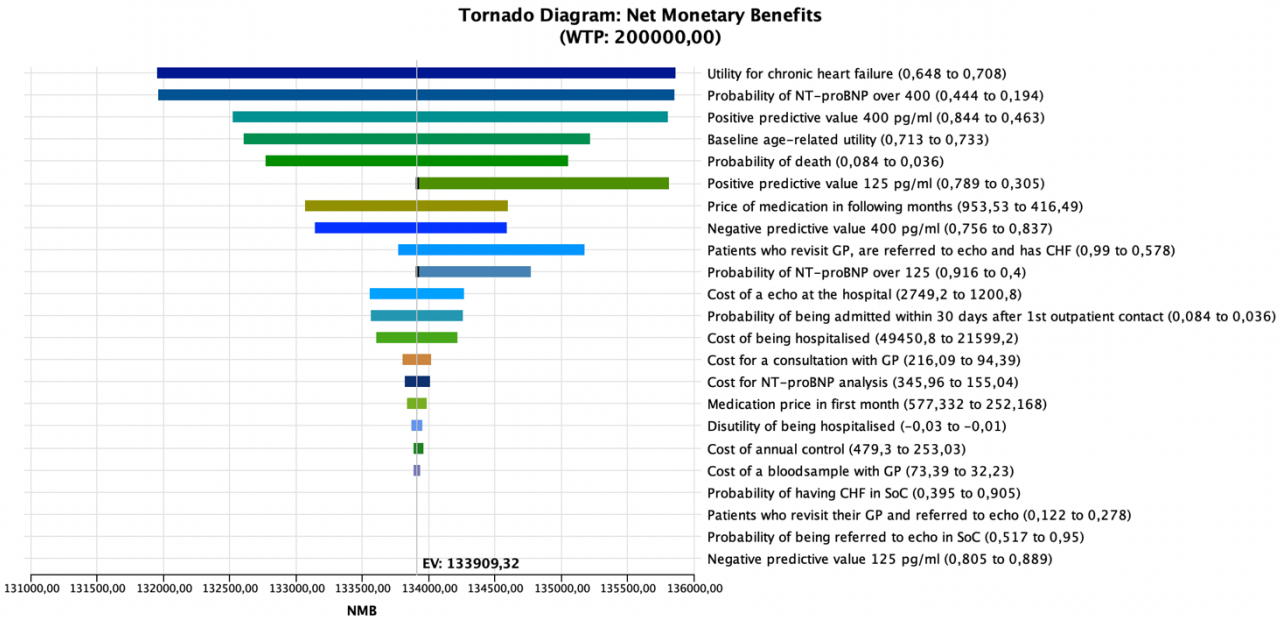

Figure 4.1. The figure illustrates the result of the one-way deterministic sensitivity analysis presented as a Tornado diagram based on net monetary benefit with a willingness-to-pay threshold of DKK 200,000. The width of the bars represents the uncertainty related to the input variable meaning that the variable with the widest bar is associated with the greatest uncertainty.

4.3. Probabilistic sensitivity analysis

The PSA was utilised to evaluate the impact of uncertainty on the base-case analysis of all input parameters simultaneously.

4.3.1. Cost-effectiveness scatter plot

The cost-effectiveness scatter plot of the 10,000 iterations for the three strategies revealed that the standard of care strategy (blue) was associated with the most significant uncertainty due to the greatest spread of iterations, indicating more parameter uncertainty with this strategy compared to the other strategies (turquoise and green). The spread of the two NT-proBNP strategies is slighter and illustrated as a horizontal ellipse meaning that the uncertainty is greater with the effectiveness compared to the cost, however, the iterations for the NT-proBNP threshold of 400 pg/ml are placed within the smallest area indicating the smallest uncertainty (see *Figure 4.2.*).

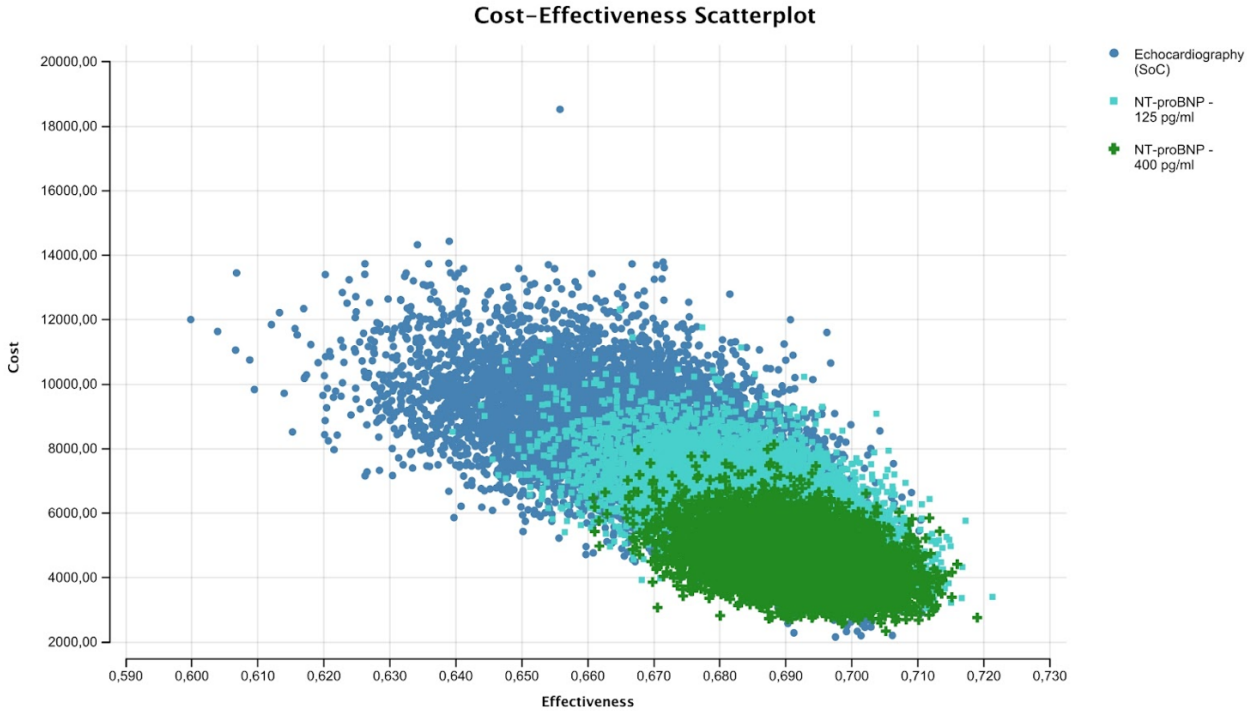

Figure 4.2. The figure depicts a cost-effectiveness scatter plot with 10,000 iterations for each of the three strategies, including standard of care (blue), NT-proBNP at a threshold of 125 pg/ml (turquoise), and NT-proBNP at a threshold of 400 pg/ml (green).

4.3.2. Cost-effectiveness acceptability curve

A CEAC was used to illustrate the likelihood of each intervention being cost-effective at increasing WTP thresholds based on the PSA (see *Figure 4.3.*). The CEAC indicates that at WTP thresholds of DKK 0 and DKK 200,000, the probability of NT-proBNP 400 pg/ml being cost-effective is 89.52% and 80.73%, respectively. Furthermore, at a WTP threshold of DKK 0, the probability of NT-proBNP 125 pg/ml and the standard of care was 7.56% and 2.92%, respectively, and at a WTP threshold of DKK 200,000, the probability was 16.06% and 3.21%. The CEAC suggests that the probability is slightly decreasing as the WTP increases for the NT-proBNP 400 pg/ml threshold (green), whereas the probability of NT-proBNP 125 pg/ml threshold (turquoise) being cost-effective is increasing.

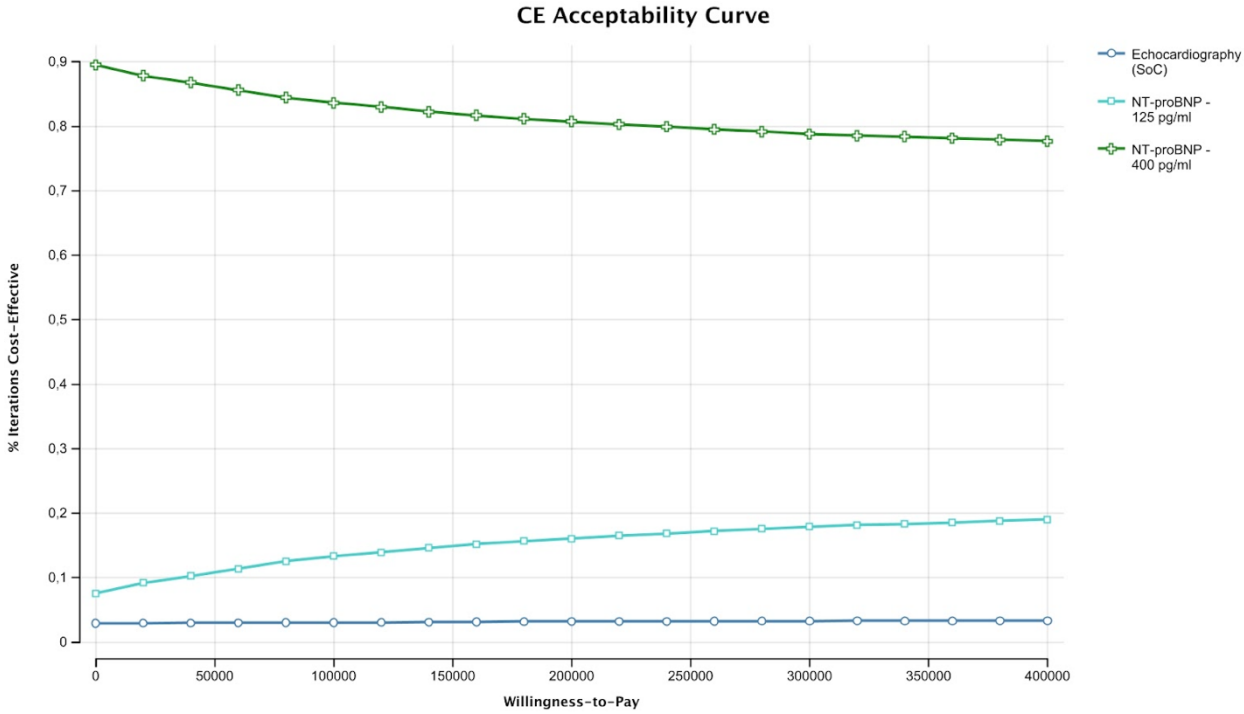

Figure 4.3. The figure depicts the cost-effectiveness acceptability curve based on the probabilistic sensitivity analysis. The curve illustrates the probability of each of the three strategies including standard of care (blue), NT-proBNP at a threshold of 125 pg/ml (turquoise), and NT-proBNP at a threshold of 400 pg/ml (green) being cost-effective.

4.4. Budget-impact analysis

A BIA was utilised to explore the annual costs related to heart failure and the potential savings of using NT-proBNP at different thresholds compared to the standard of care. The results of the BIA are presented in *Table 4.2*, and an overview of calculations can be found in *Appendix E*. The BIA estimates a total saving of approximately DKK 2.1 million over five years if the NT-proBNP threshold of 125 pg/ml is used as an initial rule-out biomarker versus standard of care. Furthermore, the BIA estimates that using an NT-proBNP threshold of 400 pg/ml instead of the standard of care will save approximately DKK 59.3 million over a five-year period and an additional saving of approximately DKK 57.2 million compared to the threshold of 125 pg/ml over the same period.

Table 4.2. The table illustrates the results of the budget-impact analysis including the accumulated annual cost as well as the cost differences in the particular year and over the entire period compared to the standard of care.

		Scenario 1 (SoC)	*Scenario 2 (125 pg/ml)*	*Scenario 3 (400 pg/ml)*
Year 1				
	Total cost (DKK)	43,138,340.00	42,729,143.34	31,514,111.96
	Differences in cost	-	*- 409,196.66*	*- 11,624,228.04*
Year 2				
	Total cost (DKK)	43,569,723.40	43,156,434.78	31,829,253.08
	Differences in cost year 2	-	*- 413,288.62*	*- 11,740,470.32*
	Differences in cost accumulated	-	*- 822,485.28*	*- 23,364,698.37*
Year 3				
	Total cost (DKK)	44,005,420.63	43,587,999.12	32,147,545.61
	Differences in cost year 3	-	*- 417,421.51*	*- 11,857,875.03*
	Differences in cost accumulated	-	*- 1,239,906.79*	*- 35,222,573.39*
Year 4				
	Total cost (DKK)	44,445,474.84	44,023,879.12	32,469,021.06
	Differences in cost year 4	-	*- 421,595.72*	*- 11,976,453.78*
	Differences in cost accumulated	-	*- 1,661,502.52*	*- 47,199,027.17*
Year 5				
	Total cost (DKK)	44,889,929.59	44,464,117.91	32,793,711.27
	Differences in cost year 5	-	*- 425,811.68*	*- 12,096,218.31*
	Differences in cost accumulated	-	*- 2,087,314.20*	*- 59,295,245.48*

Abbreviations: 125 pg/ml, NT-proBNP with a threshold of 125 pg/ml; 400 pg/ml, NT-proBNP with a threshold of 400 pg/ml; SoC, standard of care.

4.4.1. Scenario analysis

It is expected that the price of blood sample analysis will decrease significantly as more samples are run if NT-proBNP is implemented, why a scenario analysis with a sample price of DKK 53 was performed. The scenario analysis suggests a total saving of approximately DKK 25.8 million and DKK 83.0 million for the NT-proBNP threshold of 125 pg/ml and 400 pg/ml compared to the standard of care over a five-year period, respectively (see *Table 4.3.*). The calculations can be found in *Appendix F*.

Table 4.3. The table illustrates the results of the scenario analysis with lower costs of the analysis of blood samples. The analysis includes the accumulated annual cost as well as the cost differences in the particular year and over the entire period compared to the standard of care.

		Scenario 1 (SoC)	***Scenario 2 (125 pg/ml)***	***Scenario 3 (400 pg/ml)***
Year 1				
	Total cost (DKK)	43,138,340.00	38,083,143.34	26,868,111.96
	Differences in cost	-	*- 5,055,196.66*	*- 16,270,228.04*
Year 2				
	Total cost (DKK)	43,569,723.40	38,463,974.78	27,136,793.08
	Differences in cost year 2	-	*- 5,105,748.62*	*- 16,432,930.32*
	Differences in cost accumulated	-	*- 10,160,945.28*	*- 32,703,158.37*
Year 3				
	Total cost (DKK)	44,005,420.63	38,848,614.52	27,408,161.01
	Differences in cost year 3	-	*- 5,156,806.11*	*- 16,597,259.63*
	Differences in cost accumulated	-	*- 15,317,751.39*	*- 29,300,417.99*
Year 4				
	Total cost (DKK)	44,445,474.84	39,237,100.67	27,682,242.62
	Differences in cost year 4	-	*- 5,208,374.17*	*- 16,793,232.22*
	Differences in cost accumulated	-	*- 20,526,125.56*	*- 66,063,650.22*
Year 5				
	Total cost (DKK)	44,889,929.59	39,629,471.68	27,959,065.04
	Differences in cost year 5	-	*- 5,260,457.91*	*- 16,930,864.54*
	Differences in cost accumulated	-	*- 25,786,583.47*	*- 82,994,514.76*

Abbreviations: 125 pg/ml, NT-proBNP with a threshold of 125 pg/ml; 400 pg/ml, NT-proBNP with a threshold of 400 pg/ml; SoC, standard of care.

5. Discussion

The following section is a discussion of the results, strengths, and weaknesses of the choice of method as well as further considerations.

5.1. Statement of principal findings

The base case analysis indicated that the NT-proBNP 400 pg/ml strategy was less costly and more effective compared to the other strategies with a robust result to uncertainties. Over a five-year period, the implementation of NT-proBNP will reveal a saving of DKK 2-60 million depending on the NT-proBNP threshold compared to the current Danish standard practice in primary care.

5.2. Strengths and weaknesses of the study

The ability to create a simplification of the world is one strength of a decision tree, though the real world reflecting suspected heart failure may be more complex than the model can contain. The analysis is conducted from a healthcare perspective as the costs related to heart failure patients and the clinical procedure primarily fall within this perspective. However, a societal perspective is preferred in health economics as it allows for a more comprehensive cost assessment why it is debatable what additional value this could have added (Kristensen & Sigmund 2017). As mentioned, heart failure is a chronic disease that progresses over time, which in some cases also affects the ability to work, leading to productivity loss due to absenteeism and/or presenteeism (Drummond et al. 2015). Though it can be discussed whether individuals within this range of age are still in employment as the average age of being diagnosed with heart failure in Denmark is 72 years and whether the inclusion of productivity loss would have changed the base-case result (Kjærgaard 2021). In Denmark, the Danish Medicines Council recommends a restricted societal perspective excluding productivity costs as it is associated with ethical dilemmas and differences in the calculation approach of productivity costs (Danish Medicines Council 2021).

Rehabilitation and municipality care may become a necessity depending on the severity and progression of the disease, resulting in additional costs for municipalities that were not considered in this CUA. Also, patient costs (e.g., transport) were not accounted for in the model. Despite the aforementioned, it is not expected that including these costs would have affected the strategy deemed cost-effective, though it might increase the costs related to a missed diagnosis. Furthermore, the model was constructed with a one-year time horizon, and it is arguable whether this covers all relevant

costs and effects of implementing NT-proBNP in the Danish primary care setting. Nevertheless, the model is able to establish the short-term consequences and support the annual benefits of implementing NT-proBNP which, given the cost and consequence of one year could make the implementation more manageable for policymakers when allocating the annual hospital resources.

Moreover, the model does not distinguish between the clinical severity of heart failure, which is graded according to NYHA and is of great importance for prognosis and treatment selection (Løgstrup et al. 2023). Nor does it take the different phenotypes or comorbidities into account. When heart failure is classified according to NYHA and the different phenotypes, the treatment will vary and with a one-year time horizon, the model does not allow for disease deterioration nor that the prognosis may worsen over time. Changes in treatment and disease deterioration may result in increased costs to society. According to a report from 2023, Denmark is among the best at treating heart failure with a 12% reduction in the mortality rate within one year of a heart failure diagnosis (Sjøgren 2023). However, approximately 10% of patients progress to advanced stages of heart failure despite optimal treatment, which may result in further complications of the disease (Løgstrup et al. 2023). The above-mentioned is likely to increase the number of admissions, medicine intake, complications, rehabilitation, and municipality care for the individual patient, which influences both costs and effects, presuming cost and effect may be under- and overestimated, respectively. However, the latter will probably affect the three strategies equally and are of minor importance for the conclusion.

Additionally, it can be discussed whether a Markov model with a lifetime horizon would have been more accurate as such a model allows for the inclusion of several health states as well as the possibility of transitioning between them. This would have given an opportunity to divide heart failure into the different NYHA classifications and different phenotypes, investigating specific threshold values for this. The transitioning between health states would allow a patient to transit between stable and unstable stages of the disease, which would allow accounting for costs and effects related to several admissions, comorbidities, complications, and increased medicine intake over a lifetime. The choice of health economic model could influence whether an NT-proBNP threshold of 400 pg/ml would remain cost-effective. However, when evaluating a screening tool compared to a new alternative, it can be argued that a decision tree with a one-year horizon is sufficient as the procedure is of short duration and it is expected that one generally receives a heart failure diagnosis within one year. Also, including subpopulations such as NYHA and phenotypes would result in a highly detailed model and when data are unavailable, further assumptions will need to be added, which increases uncertainty.

When evaluating a screening tool, it is the early and accurate diagnosis associated with faster initiation of correct treatment and slowing the development of more severe stages that is of importance (Fonseca et al. 2022; Hildebrandt et al. 2010). It is assumed that adding NYHA classes only will contribute to greater differences in costs and effects due to earlier diagnosis, only increasing the probability of NT-proBNP being more cost-effective than the standard of care.

The base-case analysis was also not adjusted for comorbidities, risk factors, sex, or age; however, these specific factors have proven to have a distinct influence on the level of NT-proBNP (Simmonds et al. 2020; Cediel et al. 2021; Welsh et al. 2022). For instance, it has been shown that obesity is a common comorbidity in HFpEF patients and is associated with lower NT-proBNP levels (Remmelzwaal et al. 2020; Clerico et al. 2018). It can be discussed if the above-mentioned is the reason for the differences and inconsistency observed for threshold values for NT-proBNP as taking all the aforementioned factors into account in a single guideline would be complex.

A position paper from the Danish Society of Cardiology (2021) suggests that when using NT-proBNP as an initial rule-out biomarker, patients with high-risk factors should be referred for an echo without an NT-proBNP analysis in an age-dependent strategy, but this was not incorporated in the model due to a lack of information on the distribution. It may, however, be associated with slightly lower costs in NT-proBNP strategies as the cost of NT-proBNP laboratory analysis will not be accounted for. Further, it is expected that these patients will have an NT-proBNP level above the thresholds, and thus have no greater impact on the conclusion.

Furthermore, the analysis included three strategies, why NMB was used even though it requires a predefined WTP threshold that does not currently exist in Denmark. In continuation, defining a WTP threshold may be difficult as it is challenging to value human lives, especially a generic threshold that covers all diseases and ages. The results, however, showed an NT-proBNP threshold of 400 pg/ml was cost-effective independent of a WTP threshold due to lower costs along with a higher effect and the CEAC suggesting a probability of NT-proBNP 400 pg/ml being cost-effective of 89.52% and 80.73% for WTP threshold of DKK 0 and DKK 200,000, respectively.

5.2.1. Discussion of the strengths and weaknesses of model inputs

Quality of life, as well as the quality of care, is an important focus in the Danish healthcare system, why new strategies should be implemented with this in mind (Aaby et al. 2022). A delayed or missed diagnosis may have a negative impact on quality of life as patients have persistent symptoms that limit their ability in daily activities. However, the model did not differentiate between when diagnoses

are obtained, instead, a similar utility for chronic heart failure was assigned to all patients. As a result, the health benefits may be skewed as more missed diagnoses may occur in the 400 pg/ml strategy and thereby have lower total health benefits, possible impacting the strategy deemed cost-effective.
Utility weights originated from Denmark, UK, and combined data from Austria and Canada, respectively. As weights may vary among countries it can be discussed whether the latter three mentioned are representative of the Danish population (Szende et al. 2014). Utility weights depend on individual preferences connected to the overall health status and can therefore be influenced by a number of variables, including quality of life, comorbidities, structure and quality of a specific healthcare system (Sullivan et al. 2011). It can, however, be emphasised that there are great similarities between Denmark and the UK, as they are both developed countries with high income per capita and a healthcare system that is organised according to the Beveridge model (Ferreira et al. 2018; The World Bank 2021). Additionally, the disutility for admission was extracted from combined Austrian and Canadian data with different healthcare systems than the Danish, but the weight was minor and had no significant impact on the results, as illustrated by a minor uncertainty in the Tornado diagram (Bachner et al. 2022). Disutility associated with an echo and a blood test was not applied as both procedures are short of duration and temporary increasing the likelihood of no significant variation. Lastly, the utility weight for chronic heart failure was extracted from Hvidberg et al. (2023) which provided EQ-5D-3L-based HRQoL, and not the novel EQ-5D-5L version of the instrument. The two instruments have identical health dimensions, but the latter mentioned extends the number of possible responses to each health dimension from three to five, providing more detailed responses. Though EQ-5D-3L can be converted into EQ-5D-5L, it would still bring some degree of uncertainty and even though EQ-5D-5L scores for heart failure do exist, they originate from other countries and Danish values were preferred.

The treatment of chronic heart failure varies greatly depending on the NYHA stage, phenotype, comorbidities, and presenting symptoms. The included costs for medicine consumption were estimated using a pragmatic approach based on a simple start-up medication regimen consistent with the approach in other economic analyses (Løgstrup et al. 2023; Monahan et al. 2017; Fonseca et al. 2022). However, whether the approach reflects Danish clinical practice is debatable as newly diagnosed patients may have coexisting comorbidities that may affect the amount of required medication (Løgstrup et al. 2023; Simmonds et al. 2020). The latter might have led to an underestimation of costs related to treatment. On the other hand, early and accurate disease detection

combined with early and accurate treatment is associated with lower costs as well-treated patients have a higher quality of life and a lower likelihood of subsequent events and thus associated costs (Monahan et al. 2017).

Neither the CUA nor the BIA account for eventual start-up costs associated with implementing NT-proBNP in the primary sector, such as education of GPs. However, a professor of cardiology at Rigshospitalet believes that this is unnecessary as GPs already have the necessary skills and knowledge required, indicating that the implementation may not require additional resources (Sundhedspolitisk Tidsskrift 2019). Furthermore, the decision tree does not account for additional working hours associated with the blood sample analysis. The additional working hours were assumed to be minor as the blood sample already is being collected and analysed in the initial clinical assessment of a patient (Løgstrup et al. 2023). Even though this additional cost may favour the standard of care, it is doubtful that it will change which alternative is deemed cost-effective.

5.3. Strengths and weaknesses in relation to other studies, discussing important differences in results

The base-case result is in accordance with the findings of Monahan et al. (2017) and the NICE guidelines suggesting that a patient should be referred for an echo if the NT-proBNP level is ≥400 pg/ml (NICE 2018). Monahan et al. (2017) and the NICE guidelines are based on data from the REFer for EchocaRdiogram (REFER) study which included patients aged ≥70 with moderate symptoms, comorbidities, and more HFpEF phenotypes than HFrEF (Monahan et al. 2027). Only 12% of the REFER cohort had HFrEF phenotype and in their sensitivity analysis, changing the proportion of HFrEF patients from 12% to 50% or above, it became more cost-effective to change the NT-proBNP threshold from 400 pg/ml to 125 pg/ml (Monahan et al. 2017). According to population surveys, it is more representative with half of the population having the HFrEF phenotype and in this case, it was shown that the total QALY increased in each diagnostic strategy due to the higher reward of correct early detection (ibid.). Furthermore, a Danish nationwide study from 2023 showed that the HFrEF is the most common heart failure phenotype in Denmark covering approximately 43% of cases in primary care settings suggesting that an NT-proBNP threshold value of 125 pg/ml could be cost-effective in Denmark (Jensen et al. 2023). Furthermore, approximately 26% of heart failure cases in primary care settings are HFpEF or HFmrEF, for which a threshold similar to the NICE guidelines may be assumed to be applicable, due to the data underlying the guidelines being primarily based on this phenotype (Jensen et al. 2023; NICE 2018). However, Remmelzwall et al. (2020) report that the

NT-proBNP level for these specific phenotypes in stable outpatients usually is low, as opposed to patients with HFrEF, and up to one-third of all HFpEF outpatients having an NT-proBNP level below the typical diagnostic threshold values in current guidelines. A meta-analysis from 2021 also found that NT-proBNP is better at detecting HFrEF than HFpEF patients in primary care and that in individuals ≥70 years of age, the ESC guideline threshold value of ≥125 pg/ml is more sensitive at detecting heart failure, than the higher level suggested by NICE guidelines (Roalfe et al. 2021). However, limited health economic evaluations comparing the different thresholds exist. The result of Roalfe et al. (2021) is based on a population of 1000 adults in which 36% have heart failure, where the ESC threshold (NPV 84.9%) would rule out heart failure in 92 more cases than the upper NICE threshold (NPV 74.7%), but more importantly, miss 113 fewer heart failure cases (ibid.). Furthermore, Roalfe et al. (2021) combine data from the REFER study and the Utrecht HartFalen Onderzoek (UHFO) study, a study from primary care in the Netherlands. The positive and negative predictive values for the NT-proBNP thresholds applied in the conducted CUA are extracted from this meta-analysis, however, given the aforementioned, it is questionable whether the outcome would have been different if the data had been based on a more representative population for the Danish population. In comparison, Taylor et al. (2022) suggests a sensitivity of 94.6% and a specificity of 50.0% for an NT-proBNP threshold value of 125 pg/ml, with positive predictive value (PPV) and NPV of 16.4% and 98.9%, respectively. The sensitivity and specificity for the NT-proBNP threshold of 400 pg/ml were 81.7% and 80.3%, respectively, with a PPV and NPV of 30.0% and 97.7% (ibid.). The study concluded that NT-proBNP is a reliable rule-out biomarker at both thresholds; however, given the aforementioned data, the 400 pg/ml cut-off value will result in one in every five patients being missed initially, while the 125 pg/ml cut-off value will result in approximately 20 additional patients requiring diagnostic assessment for each additional new heart failure diagnosis (Taylor et al. 2022). This indicates that the optimal NT-proBNP threshold is a careful balance between specificity and sensitivity, where NPV and sensitivity of the tests are the most important indicators of the test evaluation to ensure no cases are missed (Roalfe et al. 2021). Moreover, the cost of increased unnecessary referrals for an echo due to poorer specificity is a significant consideration in a resource-limited healthcare system but also how many patients with heart failure we are willing to miss (ibid.). It can be discussed whether including a strategy with a threshold of 300 pg/ml, to accommodate the suggestion for elderly patients in the position paper from the Danish Society of Cardiology (2021) with age-specific thresholds, would have challenged the current conclusion. However, Webb et al. (2018) investigated whether a threshold of 300 pg/ml for ruling out heart failure was beneficial

compared to the NICE threshold of 400 pg/ml. The study concluded that it would incur additional costs and increase workload on the heart failure team, with only one additional heart failure patient identified (ibid.). Furthermore, the economic implications of lowering the threshold would result in additional costs of approximately £42,800 for one new heart failure patient identified compared to a threshold of 400 pg/ml (ibid.). In continuation, the BIA results indicated a significant difference in yearly costs between the 125 pg/ml and 400 pg/ml NT-proBNP thresholds, however, the model did not compare the number of identified patients nor the costs for identifying an additional patient.

Furthermore, NT-proBNP has been shown to increase rapidly with age, why it can be debated whether a threshold of 400 pg/ml increases the risk of missing a true positive patient (Welsh et al. 2022). Contrary, given the high prevalence of an elevated NT-proBNP in specific age groups a threshold of 125 pg/ml is likely to lead to many unnecessary referrals for an echo, increased hospital costs, occupied specialised resources, and make screening for undiagnosed cardiac dysfunction highly inefficient, questioning whether a single threshold value can or should be applied for an entire population. In continuation, Welsh et al. (2022) concluded that an NT-proBNP ≥125 pg/ml is common in females and elderly individuals without classical cardiovascular risk factors. Therefore, they suggest a wide use must require age and sex-specific thresholds (ibid.). Noteworthy, the profoundly different anthropometry characteristics and fat distributions found in males and females might influence NT-proBNP levels (Cediel et al. 2021). According to recent findings from a general population survey revealed that the relationship between NT-proBNP and obesity had a significant sex-associated component, why one could question the conclusion of an NT-proBNP threshold of 400 pg/ml being cost-effective due to underdiagnosis (Cediel et al. 2021; Remmelzwaal et al. 2020; Clerico et al. 2018).

Several scientific investigations, particularly Danish ones, have demonstrated that it is possible to distinguish between cardiac and non-cardiac causes of shortness of breath when measuring NT-proBNP and in 2010, Hildebrandt et al. (2010) presented age-specific cut-off values for NT-proBNP levels to rule out heart failure with reduced systolic function (Goetze et al. 2006; Mogelvang et al. 2007; Zaphiriou et al. 2005). The initial threshold values by Hildebrandt et al. (2010) were, however, set low and would lead to an excessively high number of false positive measurements if applied. Recently, the Danish Society of Cardiology (2021) published age-differentiated cut-off values for a low and high probability of heart failure with reduced systolic function but also the intermediate grey area. As mentioned earlier, NT-proBNP is considerably influenced by key clinical features of HFpEF such as renal impairment, obesity, and atrial fibrillation, resulting in higher levels of NT-proBNP, but

the range of NT-proBNP in HFpEF can also extend down to normal ranges in some patients, lower than in HFrEF which, leaves one to speculate how to judge individual risks (Januzzi & Myhre 2020). PARAGON-HF and EMPEROR-preserved are two randomised studies with HFpEF patients where elevated NT-proBNP level was an inclusion criterion and an NT-proBNP level >300 pg/ml for sinus rhythm, or >900 pg/ml in atrial fibrillation was required (Solomon et al. 2019; Anker et al. 2021). This indicates that the age-differentiated thresholds suggested by the Danish Society of Cardiology (2021) can be applied for the primary assessment prior to an echo of patients with HFpEF and HFmrEF, but with renal impairment, obesity and atrial fibrillation in mind when interpreting NT-proBNP concentrations (Jørgensen et al. 2022). When attempting to come close to finding all patients with heart failure by lowering the threshold value from, for example, 400 pg/ml to 125 pg/ml, significantly more individuals will be identified as being suspected of having heart failure, when they do not. Even though life extension is included as a result of earlier diagnosis of more patients with heart failure, this health effect does not increase proportionally with the additional costs that the lower threshold value gives rise to, as related to more referrals for an echo. These costs could, however, be used elsewhere in the healthcare system why changing the current practice in Denmark by introducing age-differentiated thresholds suggested by the Danish Society of Cardiology (2021) can be considered.

5.4. Meaning of the study: possible explanations and implications for clinicians and policymakers

The Danish healthcare system is under a great amount of pressure and the debate on the state of the healthcare system has largely been about extra hands and especially about the acute shortage of nurses, a serious problem that rightly has a political focus (AbbVie 2023). In addition, there is a growing understanding that a robust healthcare system requires more than just hands in the long term (ibid.). The complexity of the crisis challenges, functions, structures, and the way health tasks are currently distributed across different sectors (ibid.). Implementing screening for suspected heart failure using NT-proBNP in general practice prior to an echo could contribute to relieving pressure on the Danish hospitals, without compromising the quality of care. Currently, 52.6% of adults in Denmark are either moderately or severely overweight (BMI ≥25), and almost one in five adults is severely overweight composing a serious challenge for the healthcare system (AbbVie 2023). As obesity is considered a significant risk factor for a large number of chronic diseases, including heart failure, the number of patients with heart failure is likely to increase in the future (ibid.). Furthermore,

a statement from the Danish Regions revealed that the waiting time for planned somatic treatment was 6.5 weeks in the 2nd quarter of 2022 and by the end of 2022, the waiting time was 45% higher than before the covid-19 pandemic and one in five patients waited more than 30 days for evaluation (ibid.). The waiting time can influence patients referred for an echo who do not suffer from heart failure by increasing unnecessary psychological stress and insecurity. Therefore, introducing NT-proBNP in general practice may benefit patients who do not have heart failure, as these patients will receive a better and faster assessment (Roalfe et al. 2021; Webb et al. 2018). The introduction of NT-proBNP may result in earlier diagnosis and initiation of appropriate treatment, based on the assumption that the incidence of heart failure will increase, and thereby increase the quality of life (Jensen et al. 2023; Løvschall et al. 2018). Furthermore, the implementation of NT-proBNP guidelines could help relieve pressure on specialised resources, alleviate waiting times, and increase equality of treatment in primary care as well as being economically attractive. Implementing new initiatives in the healthcare system can, however, be challenging as it requires GPs to be adaptable and have the time to be familiar with the guidelines. Time is a limited resource in general practice, why it is debatable whether these estimated savings will be seen as soon as NT-proBNP is implemented (Regeringen 2018). In addition, it is possible that GPs feel safer by referring for an echo due to the above-mentioned, and it can therefore be considered whether the estimated savings of up to DKK 60 million over five years suggested by the BIA gives an accurate picture of the reality. On the other hand, the result of the BIA was in accordance with a BIA from Portugal suggesting an annual saving of EUR 935,657 and EUR 2,982,443 when using NT-proBNP with the laboratory or point-of-care setting compared to the standard of care, respectively (Fonseca et al. 2022). As a result, savings accumulated over five years may exceed the suggested saving of DKK 60 million (ibid.).

5.5. Unanswered questions and future research

When reflecting on the estimated QALY differences found over a one-year time horizon, the difference is limited. For future research, it could be interesting to investigate the accumulated costs and QALY differences over a lifetime, with a focus on the long-term benefits of early and accurate diagnosis, using a Markov model with a broad societal perspective including productivity costs. Thus, the potential benefits of implementing NT-proBNP across the primary, secondary, and tertiary sectors can be highlighted. In continuation, it would be ideal to collect Danish data for all input parameters with possible inclusion of micro costing to ensure that the model is representative of the Danish population.

Also, investigating different NT-proBNP threshold values depending on relevant risk factors, comorbidities, age, and sex may be of high interest with the trade-off between diagnostic accuracy (sensitivity) and cost-effectiveness in mind.

Furthermore, it would be interesting to investigate whether routine measurement of NT-proBNP in general practice can reduce the number of admissions, as it is assumed that more patients will receive a better investigation, and thus receive optimal treatment earlier.

Lastly, it would be of relevance to interview policymakers within the Danish regions and conduct a qualitative investigation of GPs' attitudes towards the use, as well as the implementation, of NT-proBNP in general practice. Interviewing physicians who are the final consumer of the product would give an insight into whether they are willing to use it.

6. Conclusion

In conclusion, the Master's thesis revealed that implementing NT-proBNP as a rule-out biomarker is cost-effective in Danish primary care settings. The estimated costs and QALYs accumulated to DKK 4,482, DKK 6,025, and DKK 7,913 and 0.692, 0.686, and 0.670 QALY for the NT-proBNP 400 pg/ml, NT-proBNP 125 pg/ml, and standard of care strategy, respectively. Conclusively, the NT-proBNP 400 pg/ml strategy with the lowest cost and highest effect is cost-effective from a healthcare perspective over a one-year period. In addition, the BIA revealed a total saving of DKK 2-60 million over a five-year period depending on the threshold level, potentially increasing to above DKK 80 million if the costs for the NT-proBNP laboratory analysis decrease. Even though the NT-proBNP 400 pg/ml threshold is deemed cost-effective, it might be associated with a higher risk of missing a diagnosis due to interpersonal differences, comorbidities, phenotypes, and risk factors. Therefore, choosing a specific threshold for an entire population is challenging and depends on the trade-off between unnecessary echos and missed diagnoses. Further research is required to define a clinically actionable threshold, or possible range of thresholds, for the general population, with the above-mentioned factors in mind when evaluating NT-proBNP concentrations.

7. Perspective

The Danish healthcare system has undergone significant centralisation and specialisation since the municipality reform in 2007 (Indenrigs- og Sundhedsministeriet 2018). One notable outcome of this reform was the establishment of six new super hospitals, facilitated by the Danish Quality Foundation(ibid.). These hospitals bring together various medical specialities, improving patient care and treatment. However, this centralisation has also meant that treatment is now further away from patients in several exterior areas. Patients with an established diagnosis of chronic heart failure are receiving most of their care within the municipalities, through specialised district nurses in primary care. These patients are referred to secondary care in case of acute deterioration, which may result in long, exhausting, and expensive hospital admissions. Consequently, there is a great clinical need for early detection before an admission become necessary, allowing these patients to be treated in their own homes. Several studies have investigated the use of point-of-care-testing (POCT) as part of routine heart failure monitoring in primary care (Sergi 2022; Chami et al. 2022). BNP and NT-proBNP have demonstrated similar predictive value in heart failure. NT-proBNP, in particular, has advantages such as less biological variation and greater stability, when stored at room temperature, making it an attractive biomarker for routine monitoring (Cami et al. 2022). POCT allow testing to be conducted close to the patient, enhancing the quality of patient care, while meeting hospital and laboratory accreditation standards (Sergi 2022; Chami et al. 2022). The rapid result of POCT can aid in reducing hospital admissions and improve patient care in the immediate clinical decision-making (ibid.). Furthermore, POCT has been shown to be less costly and more accessible in terms of instrument costs, personnel, and time, making implementation in primary care less costly than laboratory testing, thereby reducing the resource strain on Danish hospitals (Chami et al. 2022). Importantly, physicians have shown willingness to utilise POCT to improve the care of more than one-third of patients with heart failure (ibid.). The approach and the current state of the healthcare system support the need to rethink the process for patients with chronic heart failure, with a focus on more treatments to take place within primary care, placing greater emphasis on primary care, including GPs and municipalities. Thus, by shifting more treatments to primary care, patients can avoid unnecessary follow-ups and have more personalised and human-centred care, leaving an opportunity for the patient to be more of a human and less of a patient.

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Appendices